Conventional and Genetic Evidence on the Association between Adiposity and CKD

Pengfei Zhu,[1,2] William G. Herrington,[1,2,3] Richard Haynes,[1,2,3] Jonathan Emberson,[1,2,4] Martin J. Landray,[1,2,4,5,6] Cathie L.M. Sudlow,[7] Mark Woodward,[8,9,10] Colin Baigent,[1,2] Sarah Lewington,[2] and Natalie Staplin[1,2,4]

Due to the number of contributing authors, the affiliations are listed at the end of this article.

ABSTRACT

Background The size of any causal contribution of central and general adiposity to CKD risk and the underlying mechanism of mediation are unknown.

Methods Data from 281,228 UK Biobank participants were used to estimate the relevance of waist-to-hip ratio and body mass index (BMI) to CKD prevalence. Conventional approaches used logistic regression. Genetic analyses used Mendelian randomization (MR) and data from 394 waist-to-hip ratio and 773 BMI-associated loci. Models assessed the role of known mediators (diabetes mellitus and BP) by adjusting for measured values (conventional analyses) or genetic associations of the selected loci (multivariable MR).

Results Evidence of CKD was found in 18,034 (6.4%) participants. Each 0.06 higher measured waist-to-hip ratio and each 5-kg/m^2 increase in BMI were associated with 69% (odds ratio, 1.69; 95% CI, 1.64 to 1.74) and 58% (1.58; 1.55 to 1.62) higher odds of CKD, respectively. In analogous MR analyses, each 0.06–genetically-predicted higher waist-to-hip ratio was associated with a 29% (1.29; 1.20 to 1.38) increased odds of CKD, and each 5-kg/m^2 genetically-predicted higher BMI was associated with a 49% (1.49; 1.39 to 1.59) increased odds. After adjusting for diabetes and measured BP, chi-squared values for associations for waist-to-hip ratio and BMI fell by 56%. In contrast, mediator adjustment using multivariable MR found 83% and 69% reductions in chi-squared values for genetically-predicted waist-to-hip ratio and BMI models, respectively.

Conclusions Genetic analyses suggest that conventional associations between central and general adiposity with CKD are largely causal. However, conventional approaches underestimate mediating roles of diabetes, BP, and their correlates. Genetic approaches suggest these mediators explain most of adiposity-CKD–associated risk.

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The prevalence of obesity is high and rising in many parts of the world,[1,2] and this seems to account for some of the parallel increase in the age-adjusted prevalence of CKD.[3] Measures of general adiposity (*e.g.*, body mass index [BMI])[4–9] and central adiposity (*e.g.*, waist-to-hip ratio[10] and waist circumference[9]) have been positively associated with risk of CKD. Similar sized BMI-CKD associations have been observed in people with and without diabetes and among those with and without high BP,[4,5] and waist-to-hip ratio–CKD associations remain after adjustment for diabetes and BP.[10] These observations raise a hypothesis that obesity mediates CKD risk through mechanisms independent of its known effects on risk of type 2 diabetes and BP.[10,11]

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P.Z., W.G.H., S.L., and N.S. contributed equally to this work.

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Correspondence: Dr. William G. Herrington, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford OX3 7LF, UK. Email: will.herrington@ndph.ox.ac.uk

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An alternative explanation, however, is residual confounding due to incomplete adjustment for type 2 diabetes and BP as a result of measurement error, or unmeasured confounding factors. The existence of other biases may also explain the flattening of adiposity-CKD associations in high-risk cohorts, and the higher risk of CKD among people with the lowest levels of BMI, with consequent J- or U-shaped associations.[9]

Genetic polymorphisms associated with adiposity are allocated randomly at conception, and their associations with CKD may be less susceptible to confounding or reverse causation.[12] This can be used in a genetic epidemiologic approach referred to as Mendelian randomization (MR), the results of which may help to assess "causal" claims for a risk factor.[13,14] Analogous to classic epidemiologic approaches, a multivariable approach can be applied to MR experiments,[15] allowing estimation of the independent associations of general and central adiposity measures with CKD. Similarly, multivariable MR can assess whether, and by how much, adiposity-CKD associations are mediated by genetically determined type 2 diabetes and BP.

UK Biobank is a large prospective cohort study in an, on average, overweight population with genotyping data and baseline estimates of kidney function and albuminuria. We aimed to use data from UK Biobank to perform parallel conventional and genetic epidemiologic analyses to address the current uncertainties surrounding adiposity and CKD more definitively than previously possible. Our primary aims were to assess whether adiposity-CKD associations may be causal and by how much the known effect of adiposity on diabetes and BP may explain any causal associations with CKD. The secondary aims included assessing whether associations between central adiposity and CKD are independent of general adiposity (and vice versa) and by how much the associations between each adiposity measure (independent of the other) and CKD are mediated through diabetes and BP (Box 1).

Significance Statement

Conventional epidemiology associates increased body mass index (BMI) with higher risk of CKD. Diabetes and high BP explain half of the association. However, residual confounding factors preclude causal inferences and impede mediation assessments. A genetic approach (Mendelian randomization) may overcome these limitations. Analyses of 281,228 genotyped UK Biobank participants identified positive independent genetic associations between central and general adiposity with CKD, suggesting both are causal risk factors. Conventional approaches underestimate the role of known mediators. Diabetes and BP (and correlates) explain >80% of genetic associations between waist-to-hip ratio and CKD and two-thirds between BMI and CKD. In people without diabetes, obesity appeared to cause CKD. BP accounted for about half of the BMI-CKD associations.

METHODS

Study Population

UK Biobank is a large prospective cohort study of 502,650 middle-aged adults aged 40–69 years recruited between 2006 and 2010 in 22 assessment centers across the United Kingdom. Data include self-completed touch-screen questionnaires, computer-assisted interviews, physical and functional measurements, and biochemical assays. Genome-wide genotyping was performed in the whole cohort using the Affymetrix UK BiLEVE Axiom array and the Affymetrix UK Biobank Axiom array, and the UK Biobank genotype data were imputed with IMPUTE4 using the Haplotype Reference Consortium and the UK 10K and 1000 Genomes phase 3 reference panels.[16] A repeat assessment was conducted among a subsample of approximately 5% of the participants in 2012–2013. Detailed descriptions of UK Biobank are provided elsewhere.[17]

All analyses (conventional and genetic) used the same study population of nonrelated White British participants (n=375,351) and the same exclusions, which were those who withdrew their data (n=133); those with extreme BMI (<15 or >60 kg/m^2, n=77); and those with missing data on adiposity measures (n=9221), BP (n=1757), glycosylated hemoglobin (HbA1c; n=30,878), or albuminuria or eGFR (n=11,655) at baseline (lower limit of detection for urinary albumin =6.7 mg/L). To reduce the potential for bias due to preexisting disease, those with self-reported cancer (n=38,516), chronic obstructive pulmonary disease (n=1563), or liver cirrhosis/liver failure (n=323) at baseline were also excluded.

Exposures and Covariates

For conventional and genetic analyses, waist-to-hip ratio and BMI were selected as the measures of general and central adiposity, respectively, due to their widespread use, low correlation (r=0.46 for women and 0.60 for men in UK Biobank), and the existence of relevant genome-wide association studies (GWAS).[18,19] Potential confounders were identified on the basis of the assumed pathways between adiposity (the exposure) and CKD (the outcome) and included, from the recruitment assessment, age, education (college/university degree, A levels/AS levels or equivalent, O levels/CSEs/NVQ/others, none of the above, prefer not to answer), Townsend index of social deprivation (fifths), smoking (current smoker, previous smoker, never smoker, prefer not to answer/missing), and physical activity (<10, ≥10–<50, ≥50 metabolic equivalents h/wk). Models adjusting for mediators included diabetes status (self-reported diabetes mellitus or HbA1c≥6.5%, prediabetes [HbA1c between 5.7% and <6.5%], no diabetes [HbA1c<6.5%]), duration of diabetes (years), systolic BP (SBP; millimeters of mercury), and diastolic BP (DBP; millimeters of mercury) at baseline.

For the genetic analyses, instruments for waist-to-hip ratio and BMI were derived using independent single-nucleotide polymorphisms (SNPs; R^2<0.1; separated by 1000 kb) identified from the most recent GWAS, which have combined data from multiple studies,[18,19] with UK Biobank contributing nearly two-thirds of participants (Table 1). From these GWAS, 394 SNPs (explaining 2.5% of the variance in men

Box 1. Conceptual framework for the conventional and genetic epidemiologic analyses of adiposity and CKD outcomes

Framework
Primary aims
Aim 1: To quantify associations of adiposity measures (waist-to-hip ratio or BMI) with CKD
Models
1.1. Confounder adjusted (conventional)[a]
1.2. MR with basic adjustment (genetic)[b]
Aim 2: To assess how much adiposity-CKD associations are mediated by diabetes and BP
Models
2.1. Model 1.1 adjusted for mediators measured at baseline (conventional)[c]
2.2. Model 1.2 adjusted for mediators using genetic effects of adiposity-specific SNPs (genetic)[d]
Secondary aims
Aim 3: To quantify associations of adiposity measures with CKD, independent of the other reciprocal adiposity measure (*i.e.*, waist-to-hip ratio adjusted for BMI, and vice versa)
Models
3.1. Model 1.1 adjusted for reciprocal adiposity measured at baseline (conventional)
3.2. Model 1.2 adjusted for reciprocal adiposity using genetic effects of adiposity-specific SNPs (genetic)
Aim 4: To assess by how much associations of independent adiposity measures with CKD outcomes are mediated by diabetes and BP
Models
4.1. Model 3.1 adjusted for mediators measured at baseline (conventional)[c]
4.2. Model 3.2 adjusted for mediators using genetic effects of adiposity-specific SNPs (genetic)[d]

[a]Conventional confounder-adjusted models included age, region, deprivation index, smoking, and physical activity.
[b]Genetic basic-adjusted models included the top 40 principal components and genotyping array.
[c]Conventional mediator-adjusted models further adjusted for directly measured diabetes status and SBP/DBP.
[d]Genetic mediator-adjusted models further adjusted for the adiposity-specific SNP effects on risk of type 2 diabetes and SBP/DBP.

and 5.3% of variance in women) and 773 SNPs (explaining 6.1% of the variance in men and 5.5% of variance in women) were associated with waist-to-hip ratio and BMI, respectively, at $P<5\times10^{-9}$ (Supplemental Figures 1 and 2). These SNPs were combined into sex-specific genetic risk scores for waist-to-hip ratio and BMI. The genetic risk scores were normally distributed and used in individual-level data analyses by calculating the sum of SNP dosage for each participant. To reduce possible biases introduced by using the same population for GWAS and MR analyses, weights for SNP-specific effect sizes were extracted from non–UK Biobank sources wherever possible. Sex-specific effects of adiposity-selected SNPs on adiposity measures were extracted from the European-descendent participants of an earlier Genetic Investigation of Anthropometric Trait Consortium meta-analysis.[20,21] For the multivariable MR analyses adjusting for effect mediators (aims 2.2 and 4.2), genetic effects of the selected adiposity-associated SNPs on type 2 diabetes, SBP, and DBP were included in models. The effect of each adiposity-related SNP on type 2 diabetes risk was estimated using weights taken from European-descendent participants of the Diabetes Genetics Replication and Meta-Analysis consortium,[22] and SNP effects on BP identified by SNP-specific linear regression from UK Biobank, with adjustments for age, age squared, sex, the top 40 ancestry-based principal components, and the genotyping array (Table 1). The results of sex-combined GWAS was used for the type 2 diabetes and BP weights as effect sizes did not differ importantly by sex.

Outcomes

Because it is considered that adiposity can potentially cause intraglomerular hypertension (detectable as albuminuria), and subsequently progressive loss of kidney function, the primary outcome (referred to as "CKD") was a composite defined as long-term RRT, or a Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR calculated from both serum cystatin C and creatinine <60 ml/min per 1.73 m^2, or a spot urinary albumin-creatinine ratio ≥3 mg/mmol.[23] Sensitivity analyses for these outcomes included analyses (*1*) by two components of this outcome (*i.e.*, those outcomes on the basis of kidney function and those on the basis of albuminuria, considered separately) and (*2*) using CKD-EPI eGFR calculated from creatinine alone and by cystatin C alone.

Statistical Analyses

For conventional epidemiologic analyses, logistic regression was used to estimate the sex-specific associations of waist-to-hip ratio and BMI with prevalence of the CKD outcomes. Overall estimates were calculated by taking the inverse variance-weighted average of these sex-specific estimates. For primary aims, models were first adjusted for potential confounders (aim 1.1) and were then adjusted for the mediators, including diabetes and measured BP (aim 2.1). For secondary aims, models were adjusted for potential confounders and reciprocal adiposity (*i.e.*, waist-to-hip ratio adjusted for BMI and vice versa; aim 3.1) and were additionally adjusted for the mediators (aim 4.1) (Box 1).

To account for measurement error,[24] log odds of any CKD were plotted against the mean adiposity measures at resurvey by fifths of waist-to-hip ratio and BMI in men and women, and odds ratios (ORs) per incremental increase in measured adiposity measure were derived from the exponential of the

Table 1. Sources of European ancestry genetic data used for genetic analyses

Exposures & Mediators	Adiposity-Specific SNP Selection			Weights for Adiposity-Specific SNP Effects	
	Data Source	No. of SNPs Selected	Sample Size	Data Source	Sample Size
Exposures					
Waist-to-hip ratio	GWAS[18]	394	485,486 UK Biobank participants 212,248 other study participants (GIANT)	Non–UK Biobank GWAS[21]	212,248 participants (94,434 men, 118,004 women) from 101 studies (GIANT)
BMI	GWAS[19]	773	456,426 UK Biobank participants 322,154 other study participants (GIANT)	Non–UK Biobank GWAS[20]	322,154 participants (152,893 men, 171,977 women) from 125 studies (GIANT)
Mediators					
Type 2 diabetes mellitus	—	394 for waist-to-hip ratio, 773 for BMI	—	Non–UK Biobank GWAS[22]	26,676 cases and 132,532 controls from 18 studies (DIAGRAM)
BP	—		—	SNP-specific linear regression on BP with adjustments for age, age^2, sex, top 40 principal components, and array	281,228 UK Biobank participants[a]

Sex-specific effects of adiposity-selected SNPs on adiposity measures were used. GIANT, Genetic Investigation of Anthropometric Traits consortium; —, not applicable; DIAGRAM, Diabetes Genetics Replication and Meta-Analysis consortium.
[a]UK Biobank used for adiposity-specific SNP weights for BP as appropriate publicly available data from other sources were unavailable.

slope of inverse variance-weighted regression line across the top four-fifths of adiposity by sex. This approach was taken as other cohorts have found that intraindividual variation in adiposity measures does not change over time,[25] suggesting measurement error accounts for the majority of the apparent intraindividual variation. SDs are reduced after taking account of measurement error and are calculated by multiplying the SD by the square root of its regression dilution ratio. BMI associations are presented per 5-kg/m^2 higher BMI, which is equivalent to increments of 1.1 times its corrected SD. To allow for comparisons between adiposity-CKD associations, waist-to-hip ratio associations are also presented per 1.1 times its corrected SD (*i.e.*, per 0.06).[26]

For genetic analyses, MR using individual-level data provided causal estimates of the associations between waist-to-hip ratio and BMI with CKD outcomes. Genetic risk scores were used as a single instrument with the ratio method used to derive the causal estimate, calculated as the ratio of the association between the genetic risk score with the outcome and its association with the adiposity measure.[12] Causal estimates were then scaled to the same per incremental increase in genotype-predicted adiposity measures as the conventional analyses (*i.e.*, per 0.06 for waist-to-hip ratio and per 5-kg/m^2 for BMI). As for the conventional analyses, sex-specific associations of waist-to-hip ratio and BMI with prevalence of the CKD were estimated and then combined using the inverse variance-weighted average of these sex-specific estimates. For MR with basic adjustment, the logistic regression with CKD outcomes and linear regression with adiposity measures were both adjusted for the top 40 principal components and the array used (aim 1.2). For multivariable MR, the regression models with CKD outcomes were additionally adjusted for the genetic effects of the SNPs on type 2 diabetes and BP (aims 2.2 and 4.2) and for the reciprocal adiposity measure (aim 3.2) (Box 1).[27]

For each model, chi-squared statistics were calculated to assess evidence of association, with proportional reductions in chi square following adjustment for potential mediators providing semiquantitative estimates of mediation, analogous to the approaches used to estimate high levels of residual confounding in conventional analyses[28] (which was later confirmed by MR experiments).[29]

Sensitivity Analyses

The key sensitivity analysis was performing analyses by diabetes status at baseline to assess associations in people without diabetes. Other sensitivity analyses included (*1*) excluding SNPs that were at, or highly correlated with, loci associated with differential expression of genes in the kidney and so, may potentially have direct effects on the kidney that are not mediated through adiposity[30]; (*2*) different CKD outcomes (see above); and (*3*) standard genetic MR methods with summary-level data to examine the robustness of the MR results to violations of the instrumental variable assumptions.[31–33] Analyses were performed in SAS version 9.4 (SAS Institute, Cary, NY) and R v3.5.1.

RESULTS

Population Characteristics

Among the 281,228 participants included in analyses, mean (SD) age was 56.6 (8.0) years, and 148,692 (53%) were

women. Five percent of the participants (n=14,825; 5.3%) had diabetes, and 6.4% (n=18,034) had evidence of CKD. Mean (SD) SBP/DBP was 138/82 (19/10) mmHg. Supplemental Tables 1 and 2 provide these and other baseline characteristics for the cohort by sex and by fifths of both measured adiposity and the genetic risk scores for adiposity.

Mean (SD) waist-to-hip ratios were 0.93 (0.06) and 0.82 (0.07) in men and women, respectively. The difference in mean waist-to-hip ratio between the top fifth and the bottom fifth of its genetic risk score was 0.03 in men and 0.04 in women (which is equivalent to 0.43 and 0.64 SDs, respectively, and 0.54 and 0.80 corrected SDs, respectively). It also predicted a 1.1-kg/m^2 higher BMI (0.23 SDs and 0.23 corrected SDs) (Table 2).

Mean (SD) BMI was 27.4 (4.7) kg/m^2, and the difference in mean BMI between the top fifth and the bottom fifth of its genetic risk score was 3.2-kg/m^2 (0.68 SDs and 0.70 corrected SDs), also predicting an increase in waist-to-hip ratio of 0.02 (0.37 and 0.26 SDs and 0.46 and 0.32 corrected SDs in men and women, respectively) (Table 2).

Table 2 presents differences in other baseline characteristics between the top and bottom fifths of each exposure. Differences in age, level of deprivation, education, smoking status, and physical activity were generally much smaller across top versus bottom fifths of the adiposity-related genetic risk scores than the top versus bottom fifths of measured adiposity, supporting the use of MR to reduce the risk of residual confounding. Nevertheless, there remained a smaller proportion of college/university degrees and nonsmokers among those with higher genetic-predicted risk of increased waist-to-hip ratio and BMI. The expected increase in prevalence of diabetes with increasing genetic-predicted risk of adiposity was observed. For example, the prevalence of diabetes increased from 3.7% in the bottom fifth to 6.7% in the top fifth of the genetic risk score for waist-to-hip ratio. In comparison, the increase in SBP between the bottom and top fifths was more modest (from 138 to 139 mm Hg).

Waist-to-Hip Ratio

In conventional analyses, there was a J-shaped association between waist-to-hip ratio and CKD, which was log linear across the top four-fifths of waist-to-hip ratio. As biases resulting from ill health may explain the flattening of associations at the lowest levels of adiposity, only the top four-fifths were used to estimate the size of associations per 0.06 increment in conventional analyses. Associations across the narrower range of waist-to-hip ratio predicted by the genetic risk score were log linear throughout, allowing regression across all participants' data (Supplemental Figure 3). In confounder-adjusted conventional analyses, each 0.06 increase in waist-to-hip ratio was associated with an OR of 1.69 (95% confidence interval [95% CI], 1.64 to 1.74; chi square =1051) compared with a more modest association in genetic analyses of an OR of 1.29 (95% CI, 1.20 to 1.38; chi square =53) (Figure 1). Further adjustment for BP and diabetes in the conventional analyses reduced the OR to 1.43 (95% CI, 1.39 to 1.48) and the chi-squared value by 56% (chi square =466) (Figure 1). Analogous genetic associations attenuated ORs substantially (OR, 1.14; 95% CI, 1.05 to 1.24), reducing the chi-squared value by 83% (chi square =9.1). This was largely accounted for by adjustment for genetically predicted risk of type 2 diabetes (Table 3; sex-specific results are provided in Supplemental Table 3).

Increased waist-to-hip ratio appeared to be causally associated with CKD independent of BMI because after adjustment for BMI, associations per 0.06 increase were 1.42 (95% CI, 1.37 to 1.47; chi square =402) and 1.19 (95% CI, 1.10 to 1.29; chi square =20) for conventional and genetic approaches, respectively. Additional adjustment of these models for diabetes and BP reduced the chi-squared values by 45% and 77%, respectively, to ORs of 1.30 (95% CI, 1.26 to 1.35; chi square =222) and 1.10 (95% CI, 1.01 to 1.20; chi square =4.7), respectively (Table 3).

BMI

In the conventional BMI analyses, there was also J-shaped association that was log linear across the top four-fifths of BMI; therefore, only the top four-fifths were used to estimate conventional associations per incremental increase in BMI, whereas log-linear associations throughout the range of genetically determined BMI studied allowed regression across all participants' data (Supplemental Figure 3). Each 5-kg/m^2 increase in BMI was associated with an OR of 1.58 (95% CI, 1.55 to 1.62; chi square =1487), compared with a corresponding OR of 1.49 (95% CI, 1.39 to 1.59; chi square =129) in genetic analyses. Further adjustment for BP and diabetes in the conventional analyses led to an OR for each 5-kg/m^2 increase of 1.38 (95% CI, 1.35 to 1.41; chi square =660) (Figure 1), which represented a 56% reduction in the chi-squared compared with the confounder-adjusted model. Further adjustment for BP and diabetes in the genetic analyses also attenuated ORs (1.30; 95% CI, 1.20 to 1.41; chi square =40), which represented a 69% reduction in the chi square (Table 3).

Increased BMI appeared to be causally associated with CKD independent of waist-to-hip ratio because after adjustment for waist-to-hip ratio, ORs for each 5-kg/m^2 increase in BMI were 1.42 (95% CI, 1.39 to 1.46; chi square =763) and 1.36 (95% CI, 1.24 to 1.49; chi square =43), respectively. Additional adjustments for diabetes and BP reduced the chi-squared value by 55% in conventional and 52% in genetic analyses to ORs of 1.28 (95% CI, 1.25 to 1.31; chi square =345) and 1.25 (95% CI, 1.14 to 1.38; chi square =20), respectively (Table 3).

Sensitivity Analyses by Diabetes

CKD was only one-quarter as prevalent in people without diabetes compared with those with diabetes. Among those without diabetes, positive genetic associations between waist-to-hip ratio and CKD were present, with point estimates suggesting weaker associations (OR, 1.14; 95% CI, 1.05 to 1.23) than in people with diabetes (OR, 1.34; 95% CI, 1.10 to 1.64).

Table 2. Baseline characteristics and differences between top and bottom fifths of measured adiposity and genetic risk score

Characteristics	All	Fifths of Measured Waist-to-Hip Ratio or Measured BMI[a]			Fifths of GRS for Waist-to-Hip Ratio or BMI[b]		
		I	V	Difference	I	V	Difference
Waist-to-hip ratio							
Exposures							
Waist-to-hip ratio							
Men	0.93 (0.06)	0.85	1.03	0.18	0.92	0.95	0.03
Women	0.82 (0.07)	0.72	0.92	0.19	0.79	0.84	0.04
BMI, kg/m^2	27.4 (4.7)	24.1	31.0	6.8	26.8	27.9	1.1
Potential confounders							
Age, yr	56.6 (8.0)	54.3	58.4	4.1	56.6	56.6	0.0
College or university degree	89,459 (10.0%)	39.6%	23.8%	−15.8%	33.8%	30.0%	−3.7%
Deprivation score	−2.4 (−3.8, 0.0)	−2.6	−2.0	0.6	−2.4	−2.3	0.1
Current smoker	28,137 (10.0%)	7.4%	12.6%	5.2%	9.4%	10.6%	1.2%
Physical activity, MET h/wk	21 (9.6, 43.6)	25.2	17.6	−7.6	21.3	21.1	−0.2
Potential effect mediators							
Diabetes[c]	14,825 (5.3%)	1.3%	10.0%	8.7%	3.7%	6.7%	2.3%
SBP, mm Hg	138 (19)	135	141	6	138	139	1
DBP, mm Hg	82 (10)	79	85	5	82	83	1
BMI							
Exposures							
Waist-to-hip ratio							
Men	0.93 (0.06)	0.88	0.99	0.11	0.92	0.95	0.02
Women	0.82 (0.07)	0.77	0.86	0.09	0.81	0.82	0.02
BMI, kg/m^2	27.4 (4.7)	22.0	34.5	12.5	25.8	29.0	3.2
Potential confounders							
Age, yr	56.6 (8.0)	55.4	56.8	1.4	56.6	56.5	−0.1
College or university degree	89,459 (10.0%)	40.7%	23.0%	−17.7%	34.0%	29.9%	−4.1%
Deprivation score	−2.4 (−3.8, 0.0)	−2.4	−1.9	0.5	−2.4	−2.3	0.1
Current smoker	28,137 (10.0%)	11.5%	9.3%	−2.2%	9.2%	10.8%	1.6%
Physical activity, MET h/wk	21.5 (9.6, 43.6)	24.5	16.6	−7.9	21.2	21.3	0.1
Potential effect mediators							
Diabetes[c]	14,825 (5.3%)	1.4%	10.5%	9.2%	3.7%	6.9%	3.2%
SBP, mm Hg	138 (19)	133	142	9	138	139	1
DBP, mm Hg	82 (10)	78	86	8	82	83	1

Differences of characteristics between top and bottom fifths of measured adiposity (waist-to-hip ratio and BMI) and GRS for adiposity are shown. Waist-to-hip ratio GRS and BMI GRS included 394 SNPs (variance explained: 2.53% in men and 5.29% in women) and 773 SNPs (variance explained: 6.14% in men and 5.54% in women), respectively. Exclusions were relatedness, non-White British, self-reported cancer, chronic obstructive pulmonary disease, or liver failure/cirrhosis, with missing values of GRS, adiposity measures, BP, albuminuria, or kidney function. GRS, genetic risk score; I, bottom fifth; V, top fifth; MET, metabolic equivalent.
[a]Data are mean (SD) and *N* (%) with adjustments for age where relevant or median (Q1, Q3).
[b]Data are mean (SD) and *N* (%) with adjustments for top 40 principal components and genotyping array or median (Q1, Q3).
[c]Diabetes is defined as self-reported diabetes or HbA1c ≥ 6.5%.

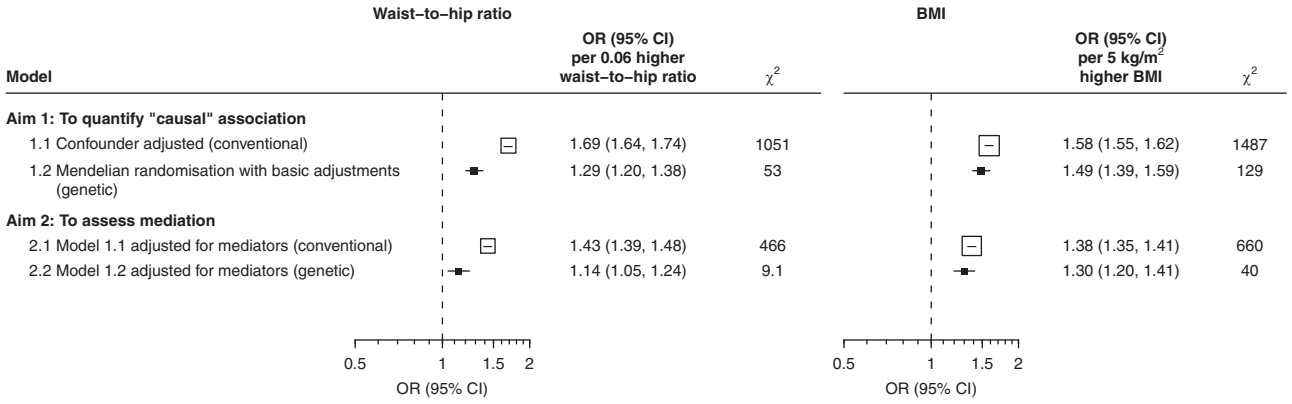
In those without diabetes, adjustment for BP reduced the chi square by 72% (from ten to three) compared with 28% in people with diabetes (from nine to six). Genetically predicted BMI was similarly strongly associated with CKD in those without diabetes (OR, 1.30; 95% CI, 1.19 to 1.41) and with diabetes (OR, 1.36; 95% CI, 1.18 to 1.56), with BP accounting for 56% and 43% of these associations, respectively (Supplemental Table 4).

Other Sensitivity Analyses

The patterns of associations between adiposity measures and CKD were generally similar when excluding 41 SNPs from BMI genetic risk score and 20 SNPs from waist-to-hip ratio genetic risk score that could be associated with differential gene expression in the kidney (Supplemental Figure 4) and in analyses on the basis of albuminuria alone, on the basis of kidney function alone, or utilizing different eGFR formulas (Supplemental Figures 5 and 6). MR Egger methods found only modest attenuation of associations (Supplemental Figure 7).

DISCUSSION

Our over-riding aim was to use genetic epidemiologic approaches to reduce biases, which can distort findings in conventional epidemiologic analyses, and therefore, assess whether previously reported relatively strong adiposity-CKD



CKD (n=18,034, 6.4%) is defined as long–term renal replacement therapy, $eGFR_{cys–cr}$ <60 mL/min/1.73m^2 or urinary albumin: creatinine ratio ≥ 3 mg/mmol.
ORs (95% CI) of any CKD per 0.06 increase in waist–to–hip ratio or per 5 kg/m^2 increase in BMI with corrections for measurement error are shown.
Adjustment for mediators were based on measures of baseline diabetes and systolic/diastolic blood pressure in conventional analyses, and the genetic effects of the adiposity–selected SNPs on type 2 diabetes and systolic/diastolic blood pressure in genetic analyses.
BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; $eGFR_{cys–cr}$: estimated glomerular filtration rate calculated from both serum cystatin C and creatinine; OR: odds ratio; SNP: single nucleotide polymorphism.

Figure 1. High waist-to-hip ratio and BMI are independent moderate "causal" risk factors for CKD. Figure 1 shows conventional and genetic associations between adiposity measures and CKD.

associations may be causal.[4–10] We found evidence that both central (*i.e.*, waist-to-hip ratio) and general adiposity (*i.e.*, BMI) seem to be independent and moderate causal risk factors for CKD. Genetic approaches estimate that each 0.06 increase in waist-to-hip ratio is associated with a 30% increased risk of CKD and that each 5-kg/m^2 higher BMI are associated with about a 50% increase in CKD risk. Genetic approaches also allow for a less confounded approach to assess mediation of associations. They suggest diabetes, BP, and their correlates account for the majority of the adiposity-CKD associations and a larger proportion than estimated by conventional approaches.

Table 3. Conventional and genetic associations between adiposity and CKD with different adjustments for reciprocal adiposity and mediators

Adjustments	Waist-to-Hip Ratio, per 0.06 Higher Level				BMI, per 5-kg/m^2 Higher Level			
	Conventional[a]		Genetic[b]		Conventional[a]		Genetic[b]	
	OR (95% CI)	Chi-Square Value (% Reduction)	OR (95% CI)	Chi-Square Value (% Reduction)	OR (95% CI)	Chi-Square Value (% Reduction)	OR (95% CI)	Chi-Square Value (% Reduction)
Confounder adjusted (aim 1)	1.69 (1.64 to 1.74)	1051.3 (Reference)	1.29 (1.20 to 1.38)	53.4 (Reference)	1.58 (1.55 to 1.62)	1486.6 (Reference)	1.49 (1.39 to 1.59)	128.9 (Reference)
+ Diabetes alone	1.50 (1.45 to 1.55)	599.6 (43)	1.17 (1.08 to 1.27)	14.4 (73)	1.45 (1.41 to 1.48)	892.6 (40)	1.35 (1.25 to 1.46)	59.2 (54)
+ BP alone	1.62 (1.57 to 1.68)	890.3 (15)	1.22 (1.13 to 1.31)	28.2 (47)	1.53 (1.49 to 1.57)	1226.7 (17)	1.40 (1.30 to 1.51)	74.8 (42)
+ Both (aim 2)	1.43 (1.39 to 1.48)	466.3 (56)	1.14 (1.05 to 1.24)	9.1 (83)	1.38 (1.35 to 1.41)	659.7 (56)	1.30 (1.20 to 1.41)	39.9 (69)
Adiposity adjusted (aim 3)	1.42 (1.37 to 1.47)	401.6 (Reference)	1.19 (1.10 to 1.29)	20.4 (Reference)	1.42 (1.39 to 1.46)	763.0 (Reference)	1.36 (1.24 to 1.49)	42.8 (Reference)
+ Diabetes alone	1.32 (1.28 to 1.37)	247.7 (38)	1.13 (1.04 to 1.23)	7.5 (63)	1.33 (1.30 to 1.37)	481.7 (37)	1.28 (1.17 to 1.41)	26.4 (38)
+ BP alone	1.40 (1.35 to 1.45)	372.7 (7)	1.14 (1.06 to 1.24)	10.8 (47)	1.38 (1.35 to 1.42)	618.9 (19)	1.31 (1.19 to 1.44)	30.6 (29)
+ Both (aim 4)	1.30 (1.26 to 1.35)	221.7 (45)	1.10 (1.01 to 1.20)	4.7 (77)	1.28 (1.25 to 1.31)	345.2 (55)	1.25 (1.14 to 1.38)	20.3 (52)

CKD (n=18,034; 6.4%) is defined as long-term RRT, eGFR calculated from both serum cystatin C and creatinine <60 ml/min per 1.73 m^2, or urinary albumin-creatinine ratio ≥3 mg/mmol. ORs (95% CIs) of any CKD per 0.06 increase in waist-to-hip ratio or per 5-kg/m^2 increase in BMI are shown. The increment for both adiposity measures equaled 1.10 times measurement error–corrected SD.
[a]For the conventional analyses, confounders include age, ethnicity, education, region, deprivation index, smoking, and physical activity at baseline.
[b]For the genetic analyses, the confounder-adjusted model was adjusted for top 40 principal components and genotyping array; other models were additionally adjusted for the genetic effects of the adiposity-selected SNPs on reciprocal adiposity (waist-to-hip ratio adjusted for BMI or vice versa), type 2 diabetes, or BP (SBP/DBP).

Among United Kingdom adults, recent data suggest about two-thirds of men and over one-half of women are overweight (*i.e.*, BMI≥25-kg/m^2) and about one-quarter of both men and women are obese (*i.e.*, BMI≥30-kg/m^2).[34] As the BMI-CKD associations from the presented genetic analyses are similar in size to associations derived from more conventional approaches, they lend support to previous prospective findings that at ages 40–79 years, about one-third of advanced CKD in the United Kingdom is attributable directly or indirectly to being overweight or obese.[4] It is conceivable that this proportion may be even larger in countries in which obesity is even more common and more limited access to treatment for diabetes and BP exists.[35]

The presented genetic analyses find conventional approaches can somewhat underestimate the potential mediating role of diabetes and its correlates. Genetic analyses adjusting for diabetes found that about half of BMI-CKD associations and three-quarters of central adiposity-CKD associations could be explained by diabetes. By virtue of any correlation between diabetes and BP, such analyses include some adjustment for BP. Adjustment for systemic BP alone explained about 45% of genetic associations. A finding that BP is of more modest importance than diabetes is consistent with other genetic studies of BP[36] and arguably, with randomized trial evidence, which estimate that a 10-mm Hg reduction in SBP may reduce albuminuria and ESKD risk by only about 10%.[37] Further characterization of the precise pathogenic mechanisms by which diabetes and its correlates (known and unknown) mediate adiposity-CKD associations is not possible using MR approaches currently. Nevertheless, large interventional trials have shown that altered intrarenal hemodynamics from both upregulated renal proximal tubular glucose resorption[38] and renin-angiotensin-aldosterone system activation[39] are key pathways that mediate diabetic kidney disease.

In people without diabetes, general population data using iohexol-measured GFR have demonstrated that central adiposity[40] and impaired fasting glucose[41] are associated with hyperfiltration. Correspondingly, UK Biobank data identify positive associations between higher adiposity levels with risk of CKD in people without diabetes or prediabetes. However, whereas CKD risk in people without diabetes was increased by 29% per 0.06-higher waist-to-hip ratio in conventional analyses adjusted for BP, only a 14% increased risk was identified from the corresponding genetic analyses. Notably, genetic analyses suggested BP explained three-quarters of this association, compared with an estimate of only one-quarter in conventional analyses (Supplemental Table 4). Genetic data, therefore, suggest that, although pathways not linked to diabetes or BP could still be responsible for mediating some of the effect of increased adiposity on CKD risk, the contribution of such pathways is substantially overestimated in conventional epidemiologic analyses.

This study benefits from UK Biobank's incredible scale and the potential for genetic approaches to better control for biases, but some limitations may exist. First, some residual biases may remain. For example, many of the SNPs used in the genetic risk scores likely affect the central nervous system rather than acting peripherally.[42,43] As well as modulating satiety, such variants could conceivably modify other behaviors that influence CKD risk. We observed that higher genetic-predicted adiposity was associated with cigarette smoking and lower educational attainment, which may result from the direct effect of SNPs rather than indirectly through the effect of SNPs on adiposity. Therefore, despite reassuring MR Egger analyses suggesting minimal evidence for pleiotropy in these analyses, the MR assumption that genetic variants are only affecting CKD risk through their effects on adiposity could be argued to be partially violated.[44] Second, whether J-shaped conventional associations at low adiposity levels result from bias could not be assessed as the genetic risk scores were an insufficiently strong tool to cover the full range of observed adiposity. Third, a large proportion of the CKD outcomes is on the basis of the presence of albuminuria, which is not as important to patients as low eGFR or the need for long-term RRT. Nevertheless, analyses on the basis of CKD outcomes derived from eGFR found associations that were, if anything, stronger than adiposity-albuminuria associations (Supplemental Figure 5), and albuminuria is such a strong predictor of advanced CKD[45] that it is part of its definition and staging.[23] Lastly, the study used a general population cohort with well-controlled BP and was restricted to people of European ancestry, and so, results may not be generalizable to other populations.

In conclusion, genetic approaches show increased central adiposity and general adiposity both seem to be independent and important causes of CKD, with associations largely explained by diabetes, BP, and their correlates.

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W. Herrington conceived the study; P. Zhu developed the study design and performed analyses under the supervision of W. Herrington, S. Lewington, and N. Staplin; M. Landray and C. Sudlow contributed to UK Biobank data collection; N. Staplin and P. Zhu had full access to the data; W. Herrington and P. Zhu wrote the first draft of the manuscript; and all authors contributed to data interpretation and revision of the manuscript.

SUPPLEMENTAL MATERIAL

This article contains the following supplemental material online at http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2020050679/-/DCSupplemental.

Supplemental Figure 1. Selection of variants for the waist-to-hip ratio genetic risk score.

Supplemental Figure 2. Selection of variants for the BMI genetic risk score.

Supplemental Figure 3. Conventional and genetic associations between adiposity measures and CKD by sex.

Supplemental Figure 4. Conventional and genetic associations between adiposity measures and CKD using GRS with exclusions of loci with differential gene expression in kidney.

Supplemental Figure 5. Conventional and genetic associations between adiposity measures and CKD by different CKD outcomes.

Supplemental Figure 6. Conventional and genetic associations between adiposity measures and CKD by eGFR formula.

Supplemental Figure 7. Genetic associations between adiposity measures and CKD using two-sample Mendelian randomization.

Supplemental Table 1. (A) Baseline characteristics by fifths of measured waist-to-hip ratio and genetic risk score (GRS) in men and (B) baseline characteristics by fifths of measured waist-to-hip ratio and GRS in women.

Supplemental Table 2. (A) Baseline characteristics by fifths of measured BMI and genetic risk score (GRS) in men and (B) baseline characteristics by fifths of measured BMI and GRS in women.

Supplemental Table 3. (A) Conventional and genetic associations between adiposity and CKD with different adjustments for reciprocal adiposity and mediators in men and (B) conventional and genetic associations between adiposity and CKD with different adjustments for reciprocal adiposity and mediators in women.

Supplemental Table 4. Conventional and genetic associations between adiposity and CKD by diabetes status with and without adjustment for BP.

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AFFILIATIONS

[1]Medical Research Council Population Health Research Unit at the University of Oxford, Nuffield Department of Population Health, Oxford, United Kingdom
[2]Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford, United Kingdom
[3]Oxford Kidney Unit, Churchill Hospital, Oxford, United Kingdom
[4]Big Data Institute, Li Ka Shing Centre for Health Information and Discovery, University of Oxford, Oxford, United Kingdom
[5]Health Data Research UK, University of Oxford, Oxford, United Kingdom
[6]National Institute for Health Research Oxford Biomedical Research Centre, University of Oxford, Oxford, United Kingdom
[7]Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, United Kingdom
[8]The George Institute for Global Health, Faculty of Medicine, University of New South Wales, Sydney, Australia
[9]The George Institute for Global Health, Nuffield Department of Women's and Reproductive Health, University of Oxford, Oxford, United Kingdom
[10]Welch Center for Prevention, Epidemiology and Clinical Research, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland

CONVENTIONAL AND GENETIC EVIDENCE ON THE ASSOCIATION BETWEEN ADIPOSITY AND CHRONIC KIDNEY DISEASE: ANALYSES FROM THE UK BIOBANK

Supplemental materials

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Supplemental table 1a: Baseline characteristics by fifths of measured waist-to-hip ratio and genetic risk score (GRS) in men

Characteristics	Fifths of measured waist-to-hip ratio †					Fifths of genetic risk score for waist-to-hip ratio ‡					Men (n=132,536)
	I	II	III	IV	V	I	II	III	IV	V	
Adiposity											
Waist-to-hip ratio	0.85 (0.02)	0.90 (0.02)	0.93 (0.02)	0.97 (0.02)	1.03 (0.02)	0.92 (0.06)	0.93 (0.06)	0.93 (0.06)	0.94 (0.06)	0.95 (0.06)	0.93 (0.06)
BMI (kg/m^2)	24.4 (3.4)	26.3 (3.4)	27.6 (3.4)	29.1 (3.4)	31.6 (3.4)	27.1 (4.1)	27.6 (4.1)	27.8 (4.1)	28.1 (4.1)	28.5 (4.1)	27.8 (4.2)
Socio-demographics											
Age, years	54.5 (8.0)	55.9 (8.0)	56.9 (8.0)	57.8 (8.0)	58.8 (8.0)	56.8 (8.1)	56.8 (8.1)	56.8 (8.1)	56.8 (8.1)	56.7 (8.1)	56.8 (8.1)
College or University degree	11,847 (43.7%)	9,990 (36.8%)	8,897 (33.0%)	7,431 (28.3%)	6,115 (23.4%)	9,566 (35.8%)	9,013 (33.9%)	8,890 (33.6%)	8,609 (32.5%)	8,202 (31.1%)	44,280 (33.4%)
Deprivation score	-2.5 (-3.9, -0.2)	-2.5 (-3.9, -0.3)	-2.5 (-3.8, -0.1)	-2.3 (-3.7, 0.2)	-2.0 (-3.5, 0.9)	-2.4 (-3.8, -0.1)	-2.4 (-3.8, 0.0)	-2.4 (-3.8, 0.1)	-2.3 (-3.7, 0.1)	-2.3 (-3.7, 0.3)	-2.4 (-3.8, 0.1)
Lifestyle											
Current smoker	2,769 (9.8%)	2,961 (10.8%)	3,130 (11.7%)	3,142 (12.2%)	3,519 (14.0%)	2,947 (11.2%)	2,971 (11.3%)	3,079 (11.6%)	3,208 (12.1%)	3,316 (12.4%)	15,521 (11.7%)
Physical activity	27.9 (13.7, 52.1)	24.5 (11.6, 48.2)	22.9 (10.3, 46.9)	20.6 (8.6, 44.0)	17.6 (7.3, 40.2)	22.4 (10.2, 45.9)	23.1 (10.1, 46.6)	23.0 (10.1, 47.1)	22.9 (9.9, 46.7)	22.8 (10.0, 47.3)	22.9 (10.0, 46.7)
Health status											
Diabetes ¶	557 (1.9%)	849 (2.7%)	1,369 (4.2%)	2,243 (6.8%)	4,350 (13.0%)	1,488 (5.6%)	1,713 (6.4%)	1,844 (6.9%)	1,962 (7.3%)	2,361 (8.8%)	9,368 (7.1%)
Any vascular diseases §	1,103 (4.7%)	1,544 (5.9%)	1,979 (7.1%)	2,508 (8.6%)	3,540 (11.5%)	1,887 (7.1%)	2,045 (7.7%)	2,108 (7.9%)	2,268 (8.5%)	2,366 (8.9%)	10,674 (8.1%)
SBP (mmHg)	138 (17)	140 (17)	142 (17)	143 (17)	143 (17)	141 (17)	141 (17)	141 (17)	141 (17)	142 (17)	141 (17)
DBP (mmHg)	81 (10)	84 (10)	85 (10)	86 (10)	86 (10)	84 (10)	84 (10)	84 (10)	84 (10)	85 (10)	84 (10)
CKD♣	949 (3.8%)	1,111 (4.1%)	1,456 (5.0%)	2,001 (6.7%)	3,312 (10.8%)	1,629 (6.2%)	1,687 (6.4%)	1,772 (6.7%)	1,766 (6.6%)	1,975 (7.4%)	8,829 (6.7%)

† Mean (SD) and N (%) with adjustments for age where relevant and median (Q1, Q3) are shown by fifths of measured waist-to-hip ratio and GRS.
‡ Mean (SD) and N (%) with adjustments for top 40 principal components and genotyping array and median (Q1, Q3) are shown by fifths of measured waist-to-hip ratio and GRS.
¶ Diabetes is defined as self-reported diabetes or HbA1c ≥6.5%.
§ Any vascular diseases include self-reported heart attack, angina, and stroke.
♣ CKD was defined as long-term renal replacement therapy, or $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m^{2}or urinary albumin:creatinine ratio ≥ 3 mg/mmol.
Exclusions: relatedness, non-White British, self-reported cancer, chronic obstructive pulmonary disease or liver failure/cirrhosis; with missing values of genetic risk score, adiposity measures, blood pressure, or chronic kidney disease.
Waist-to-hip ratio GRS included 394 SNPs (variance explained: 2.53%).
BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GRS: genetic risk score; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure.

Supplemental table 1b: Baseline characteristics by fifths of measured waist-to-hip ratio and genetic risk score (GRS) in women

Characteristics	Fifths of measured waist-to-hip ratio †					Fifths of genetic risk score for waist-to-hip ratio ‡					Women (n=148,692)
	I	II	III	IV	V	I	II	III	IV	V	
Adiposity											
Waist-to-hip ratio	0.72 (0.02)	0.77 (0.02)	0.81 (0.02)	0.85 (0.02)	0.92 (0.02)	0.79 (0.07)	0.81 (0.07)	0.82 (0.07)	0.82 (0.07)	0.84 (0.07)	0.82 (0.07)
BMI (kg/m^2)	23.9 (4.5)	25.2 (4.5)	26.8 (4.5)	28.5 (4.5)	30.4 (4.5)	26.6 (5.0)	26.8 (5.0)	27.0 (5.0)	27.1 (5.0)	27.3 (5.0)	27.0 (5.0)
Socio-demographics											
Age, years	54.2 (7.8)	55.5 (7.8)	56.5 (7.8)	57.3 (7.8)	58.1 (7.8)	56.4 (7.9)	56.4 (7.9)	56.3 (7.9)	56.3 (7.9)	56.4 (7.9)	56.3 (7.9)
College or University degree	11,223 (35.9%)	10,048 (32.9%)	9,027 (30.5%)	8,026 (27.5%)	6,855 (24.1%)	9,497 (31.9%)	9,187 (30.8%)	9,107 (30.6%)	8,812 (29.7%)	8,576 (28.9%)	45,179 (30.4%)
Deprivation score	-2.6 (-3.9, -0.5)	-2.5 (-3.8, -0.4)	-2.4 (-3.8, -0.2)	-2.3 (-3.7, 0.1)	-2.0 (-3.5, 0.7)	-2.4 (-3.8, -0.2)	-2.4 (-3.8, -0.1)	-2.4 (-3.7, 0.0)	-2.4 (-3.8, -0.1)	-2.3 (-3.7, 0.1)	-2.4 (-3.7, 0.0)
Lifestyle											
Current smoker	1,751 (5.3%)	2,292 (7.2%)	2,499 (8.3%)	2,833 (9.6%)	3,241 (11.4%)	2,333 (8.0%)	2,401 (8.1%)	2,545 (8.5%)	2,664 (8.9%)	2,673 (8.9%)	12,616 (8.5%)
Physical activity	22.9 (11.0, 44.0)	22.0 (10.1, 42.0)	20.6 (9.3, 41.2)	19.1 (8.5, 39.2)	17.6 (7.8, 37.5)	20.4 (9.2, 40.6)	20.5 (9.2, 40.6)	20.7 (9.3, 41.6)	20.8 (9.3, 41.4)	20.2 (9.1, 40.6)	20.6 (9.2, 41.0)
Health status											
Diabetes ¶	293 (0.8%)	414 (1.0%)	600 (1.5%)	1,163 (2.8%)	2,987 (7.2%)	731 (2.4%)	940 (3.1%)	1,077 (3.5%)	1,216 (4.0%)	1,493 (4.9%)	5,457 (3.7%)
Any vascular diseases §	415 (1.6%)	571 (1.9%)	790 (2.5%)	1,112 (3.2%)	1,732 (4.8%)	762 (2.6%)	884 (3.0%)	969 (3.2%)	965 (3.2%)	1,040 (3.5%)	4,620 (3.1%)
SBP (mmHg)	132 (18)	134 (18)	135 (18)	137 (18)	138 (18)	135 (19)	135 (19)	135 (19)	136 (19)	136 (19)	135 (19)
DBP (mmHg)	78 (10)	79 (10)	81 (10)	82 (10)	83 (10)	80 (10)	80 (10)	81 (10)	81 (10)	81 (10)	81 (10)
CKD♣	1,298 (4.7%)	1,474 (5.0%)	1,590 (5.2%)	1,989 (6.2%)	2,854 (8.7%)	1,718 (5.8%)	1,793 (6.0%)	1,834 (6.2%)	1,945 (6.5%)	1,915 (6.4%)	9,205 (6.2%)

† Mean (SD) and N (%) with adjustments for age where relevant and median (Q1, Q3) are shown by fifths of measured waist-to-hip ratio and GRS.
‡ Mean (SD) and N (%) with adjustments for top 40 principal components and genotyping array and median (Q1, Q3) are shown by fifths of measured waist-to-hip ratio and GRS.
¶ Diabetes is defined as self-reported diabetes or HbA1c ≥6.5%.
§ Any vascular diseases include self-reported heart attack, angina, and stroke.
♣ CKD was defined as long-term renal replacement therapy, or $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol.
Exclusions: relatedness, non-White British, self-reported cancer, chronic obstructive pulmonary disease or liver failure/cirrhosis; with missing values of genetic risk score, adiposity measures, blood pressure, or chronic kidney disease.
Waist-to-hip ratio GRS included 394 SNPs (variance explained: 5.29%).
BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GRS: genetic risk score; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure.

Supplemental table 2a: Baseline characteristics by fifths of measured BMI and genetic risk score (GRS) in men

Characteristics	Fifths of measured BMI †					Fifths of genetic risk score for BMI ‡					Men (n=132,536)
	I	II	III	IV	V	I	II	III	IV	V	
Adiposity											
Waist-to-hip ratio	0.88 (0.05)	0.91 (0.05)	0.93 (0.05)	0.96 (0.05)	0.99 (0.05)	0.92 (0.06)	0.93 (0.06)	0.93 (0.06)	0.94 (0.06)	0.95 (0.06)	0.93 (0.06)
BMI (kg/m^2)	22.8 (1.7)	25.5 (1.7)	27.3 (1.7)	29.4 (1.7)	34.1 (1.7)	26.4 (4.0)	27.2 (4.0)	27.8 (4.0)	28.3 (4.0)	29.3 (4.0)	27.8 (4.2)
Socio-demographics											
Age, years	56.2 (8.1)	56.9 (8.1)	56.9 (8.1)	57.0 (8.1)	56.9 (8.1)	56.8 (8.1)	56.9 (8.1)	56.8 (8.1)	56.7 (8.1)	56.7 (8.1)	56.8 (8.1)
College or University degree	11,561 (43.0%)	9,984 (37.4%)	8,789 (32.9%)	7,596 (28.4%)	6,350 (23.7%)	9,510 (35.7%)	9,137 (34.4%)	8,891 (33.6%)	8,568 (32.3%)	8,174 (31.0%)	44,280 (33.4%)
Deprivation score	-2.4 (-3.8, 0.2)	-2.6 (-3.9, -0.3)	-2.5 (-3.9, -0.3)	-2.4 (-3.8, 0.0)	-2.0 (-3.5, 0.8)	-2.4 (-3.8, 0.0)	-2.4 (-3.7, 0.0)	-2.4 (-0.2, 0.0)	-2.3 (-0.3, 0.2)	-2.3 (-0.1, 0.2)	-2.4 (-3.8, 0.1)
Lifestyle											
Current smoker	3,871 (14.3%)	3,046 (11.4%)	2,906 (10.9%)	2,853 (10.8%)	2,845 (10.7%)	2,907 (11.0%)	3,026 (11.4%)	3,156 (11.9%)	3,076 (11.6%)	3,356 (12.6%)	15,521 (11.7%)
Physical activity	25.1 (12.0, 48.8)	24.5 (11.3, 48.3)	23.3 (10.6, 47.6)	22.1 (9.6, 45.9)	18.3 (7.4, 41.5)	22.1 (9.9, 45.0)	22.8 (10.0, 46.6)	22.9 (52.1, 46.2)	23.1 (48.2, 47.5)	23.1 (46.9, 48.1)	22.9 (10.0, 46.7)
Health status											
Diabetes ¶	637 (2.0%)	915 (2.7%)	1,296 (3.9%)	2,060 (6.2%)	4,460 (14.1%)	1,373 (5.1%)	1,674 (6.2%)	1,819 (6.7%)	2,019 (7.5%)	2,483 (9.2%)	9,368 (7.1%)
Any vascular diseases §	1,336 (4.9%)	1,626 (5.7%)	1,983 (7.0%)	2,388 (8.5%)	3,341 (12.4%)	1,868 (7.0%)	1,966 (7.4%)	2,140 (8.0%)	2,258 (8.5%)	2,442 (9.1%)	10,674 (8.1%)
SBP (mmHg)	137 (17)	140 (17)	142 (17)	143 (17)	144 (17)	141 (17)	141 (17)	141 (17)	142 (17)	142 (17)	141 (17)
DBP (mmHg)	80 (10)	83 (10)	85 (10)	86 (10)	87 (10)	84 (10)	84 (10)	84 (10)	84 (10)	85 (10)	84 (10)
CKD♣	1,118 (4.0%)	1,235 (4.3%)	1,467 (5.1%)	1,820 (6.3%)	3,189 (11.4%)	1,495 (5.6%)	1,710 (6.4%)	1,749 (6.6%)	1,842 (6.9%)	2,033 (7.6%)	8,829 (6.7%)

† Mean (SD) and N (%) with adjustments for age where relevant and median (Q1, Q3) are shown by fifths of measured BMI and GRS.
‡ Mean (SD) and N (%) with adjustments for top 40 principal components and genotyping array and median (Q1, Q3) are shown by fifths of measured BMI and GRS.
¶ Diabetes is defined as self-reported diabetes or HbA1c ≥6.5%.
§ Any vascular diseases include self-reported heart attack, angina, and stroke.
♣ CKD was defined as long-term renal replacement therapy, or $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol.
Exclusions: relatedness, non-White British, self-reported cancer, chronic obstructive pulmonary disease or liver failure/cirrhosis; with missing values of genetic risk score, adiposity measures, blood pressure, or chronic kidney disease.
BMI GRS included 773 SNPs (variance explained: 6.14%).
BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GRS: genetic risk score; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure.

Supplemental table 2b: Baseline characteristics by fifths of measured BMI and genetic risk score (GRS) in women

Characteristics	Fifths of measured BMI †					Fifths of genetic risk score for BMI ‡					Women (n=148,692)
	I	II	III	IV	V	I	II	III	IV	V	
Adiposity											
Waist-to-hip ratio	0.77 (0.06)	0.79 (0.06)	0.81 (0.06)	0.84 (0.06)	0.86 (0.06)	0.81 (0.07)	0.81 (0.07)	0.82 (0.07)	0.82 (0.07)	0.82 (0.07)	0.82 (0.07)
BMI (kg/m^2)	21.2 (1.9)	23.9 (1.9)	26.1 (1.9)	28.8 (1.9)	34.8 (1.9)	25.4 (4.9)	26.3 (4.9)	26.9 (4.9)	27.5 (4.9)	28.7 (4.9)	27.0 (5.0)
Socio-demographics											
Age, years	54.7 (7.9)	56.0 (7.9)	56.9 (7.9)	57.3 (7.9)	56.8 (7.9)	56.3 (7.9)	56.3 (7.9)	56.4 (7.9)	56.3 (7.9)	56.4 (7.9)	56.3 (7.9)
College or University degree	11,927 (38.5%)	10,116 (33.6%)	8,691 (29.4%)	7,740 (26.5%)	6,705 (22.5%)	9,606 (32.2%)	9,296 (31.2%)	8,999 (30.2%)	8,776 (29.5%)	8,502 (28.8%)	45,179 (30.4%)
Deprivation score	-2.5 (-3.8, -0.3)	-2.6 (-3.9, -0.6)	-2.5 (-3.8, -0.3)	-2.3 (-3.7, 0.0)	-1.8 (-3.4, 1.0)	-2.5 (-3.8, -0.2)	-2.4 (-3.7, -0.2)	-2.4 (-0.5, -0.1)	-2.4 (-0.4, 0.0)	-2.3 (-0.2, 0.1)	-2.4 (-3.7, 0.0)
Lifestyle											
Current smoker	2,807 (9.0%)	2,449 (8.2%)	2,480 (8.5%)	2,513 (8.7%)	2,367 (8.1%)	2,268 (7.7%)	2,402 (8.1%)	2,554 (8.6%)	2,573 (8.6%)	2,819 (9.3%)	12,616 (8.5%)
Physical activity	24.0 (11.5, 45.5)	22.9 (10.7, 44.2)	21.0 (9.9, 41.4)	18.9 (8.4, 38.6)	15.8 (6.8, 33.4)	20.7 (9.2, 41.4)	20.7 (8.9, 41.2)	20.6 (44.0, 40.7)	20.5 (42.0, 41.1)	20.1 (41.2, 40.3)	20.6 (9.2, 41.0)
Health status											
Diabetes ¶	303 (0.8%)	417 (1.0%)	608 (1.4%)	1,129 (2.6%)	3,000 (7.3%)	760 (2.5%)	905 (3.0%)	1,028 (3.4%)	1,263 (4.1%)	1,501 (4.9%)	5,457 (3.7%)
Any vascular diseases §	429 (1.5%)	576 (1.8%)	823 (2.4%)	1,115 (3.2%)	1,677 (5.1%)	814 (2.7%)	883 (3.0%)	930 (3.1%)	934 (3.1%)	1,059 (3.5%)	4,620 (3.1%)
SBP (mmHg)	130 (17)	134 (17)	136 (17)	137 (17)	140 (17)	135 (19)	135 (19)	135 (19)	136 (19)	136 (19)	135 (19)
DBP (mmHg)	77 (9)	79 (9)	81 (9)	82 (9)	85 (9)	80 (10)	80 (10)	81 (10)	81 (10)	81 (10)	81 (10)
CKD♣	1,504 (5.3%)	1,378 (4.5%)	1,532 (4.8%)	1,872 (5.8%)	2,919 (9.4%)	1,743 (5.9%)	1,684 (5.7%)	1,877 (6.3%)	1,888 (6.3%)	2,013 (6.7%)	9,205 (6.2%)

† Mean (SD) and N (%) with adjustments for age where relevant and median (Q1, Q3) are shown by fifths of measured BMI and GRS.
‡ Mean (SD) and N (%) with adjustments for top 40 principal components and genotyping array and median (Q1, Q3) are shown by fifths of measured BMI and GRS.
¶ Diabetes is defined as self-reported diabetes or HbA1c ≥6.5%.
§ Any vascular diseases include self-reported heart attack, angina, and stroke.
♣ CKD was defined as long-term renal replacement therapy, or $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol.
Exclusions: relatedness, non-White British, self-reported cancer, chronic obstructive pulmonary disease or liver failure/cirrhosis; with missing values of genetic risk score, adiposity measures, blood pressure, or chronic kidney disease.
BMI GRS included 773 SNPs (variance explained: 5.54%).
BMI: body mass index; CKD: chronic kidney disease; DBP: diastolic blood pressure; eGFR: estimated glomerular filtration rate; GRS: genetic risk score; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure.

Supplemental table 3a: Conventional and genetic associations between adiposity and CKD with different adjustments for reciprocal adiposity and mediators in men

	Waist-to-hip ratio (per 0.06 higher level)				BMI (per 5 kg/m^2 higher level)			
	Conventional †		Genetic ‡		Conventional †		Genetic ‡	
Adjustments	**OR (95% CI)**	**χ^2 (% reduction)**	**OR (95% CI)**	**χ^2 (% reduction)**	**OR (95% CI)**	**χ^2 (% reduction)**	**OR (95% CI)**	**χ^2 (% reduction)**
Confounder adjusted (Aim 1)	2.05 (1.95, 2.15)	851.8 (ref)	1.55 (1.36, 1.76)	44.0 (ref)	1.83 (1.77, 1.90)	999.4 (ref)	1.74 (1.56, 1.94)	104.5 (ref)
+ Diabetes alone	1.77 (1.68, 1.86)	508.7 (40%)	1.26 (1.09, 1.46)	9.7 (78%)	1.61 (1.54, 1.67)	567.4 (43%)	1.52 (1.36, 1.71)	49.8 (52%)
+ BP alone	2.01 (1.92, 2.11)	801.8 (6%)	1.45 (1.26, 1.67)	27.7 (37%)	1.80 (1.73, 1.87)	920.0 (8%)	1.60 (1.43, 1.80)	62.2 (41%)
+ Both (Aim 2)	1.72 (1.63, 1.81)	453.4 (47%)	1.23 (1.05, 1.43)	6.9 (84%)	1.55 (1.49, 1.61)	479.2 (52%)	1.46 (1.29, 1.65)	34.7 (67%)
Adiposity adjusted (Aim 3)	1.60 (1.51, 1.68)	301.5 (ref)	1.36 (1.15, 1.61)	12.8 (ref)	1.56 (1.49, 1.62)	442.8 (ref)	1.56 (1.32, 1.83)	28.7 (ref)
+ Diabetes alone	1.47 (1.40, 1.56)	201.4 (33%)	1.17 (0.98, 1.40)	3.2 (75%)	1.41 (1.35, 1.47)	252.3 (43%)	1.43 (1.21, 1.68)	17.7 (38%)
+ BP alone	1.60 (1.52, 1.69)	302.0 (0%)	1.30 (1.09, 1.55)	8.6 (33%)	1.53 (1.47, 1.59)	403.3 (9%)	1.48 (1.26, 1.75)	21.9 (24%)
+ Both (Aim 4)	1.47 (1.40, 1.55)	198.6 (34%)	1.15 (0.96, 1.38)	2.3 (82%)	1.37 (1.31, 1.43)	206.8 (53%)	1.39 (1.17, 1.64)	14.7 (49%)

CKD (n=18,034, 6.4%) is defined as long-term renal replacement therapy, $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m² or urinary albumin:creatinine ratio ≥3 mg/mmol.
ORs (95% CI) of any CKD per 0.06 increase in waist-to-hip ratio or per 5 kg/m² increase in BMI are shown. The increment for both adiposity measures equalled 1.10 × measurement-error corrected standard deviation (SD).
† For the conventional analyses, confounders include age, ethnicity, education, region, deprivation index, smoking, physical activity at baseline.
‡ For the genetic analyses, confounder adjusted model was adjusted for top 40 principal components and genotyping array; other models were additionally adjusted for the genetic effects of the adiposity-selected SNPs on reciprocal adiposity (waist-to-hip ratio adjusted for BMI or vice versa), type 2 diabetes, or BP (systolic/diastolic BP).
BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Supplemental table 3b: Conventional and genetic associations between adiposity and CKD with different adjustments for reciprocal adiposity and mediators in women

	Waist-to-hip ratio (per 0.06 higher level)				BMI (per 5 kg/m^2 higher level)			
	Conventional †		Genetic ‡		Conventional †		Genetic ‡	
Adjustments	**OR (95% CI)**	**χ^2 (% reduction)**	**OR (95% CI)**	**χ^2 (% reduction)**	**OR (95% CI)**	**χ^2 (% reduction)**	**OR (95% CI)**	**χ^2 (% reduction)**
Confounder adjusted (Aim 1)	1.46 (1.40, 1.52)	308.5 (ref)	1.20 (1.11, 1.30)	20.0 (ref)	1.45 (1.40, 1.49)	581.7 (ref)	1.33 (1.22, 1.46)	38.6 (ref)
+ Diabetes alone	1.33 (1.27, 1.38)	164.5 (47%)	1.13 (1.03, 1.25)	6.1 (69%)	1.35 (1.31, 1.40)	371.0 (36%)	1.23 (1.11, 1.36)	16.6 (57%)
+ BP alone	1.38 (1.32, 1.44)	221.2 (28%)	1.14 (1.05, 1.24)	9.0 (55%)	1.38 (1.34, 1.42)	421.8 (27%)	1.27 (1.15, 1.40)	21.8 (44%)
+ Both (Aim 2)	1.25 (1.20, 1.31)	101.6 (67%)	1.10 (1.00, 1.22)	3.5 (82%)	1.28 (1.24, 1.32)	236.7 (59%)	1.20 (1.07, 1.33)	10.7 (72%)
Adiposity adjusted (Aim 3)	1.30 (1.24, 1.36)	133.9 (ref)	1.15 (1.06, 1.25)	10.6 (ref)	1.35 (1.31, 1.40)	348.6 (ref)	1.28 (1.14, 1.43)	18.0 (ref)
+ Diabetes alone	1.22 (1.17, 1.28)	74.2 (45%)	1.12 (1.01, 1.23)	4.6 (57%)	1.29 (1.25, 1.33)	239.8 (31%)	1.22 (1.08, 1.37)	11.1 (39%)
+ BP alone	1.27 (1.22, 1.33)	112.2 (16%)	1.10 (1.01, 1.21)	4.8 (55%)	1.30 (1.26, 1.34)	253.1 (27%)	1.23 (1.09, 1.38)	11.9 (34%)
+ Both (Aim 4)	1.19 (1.14, 1.25)	57.6 (57%)	1.09 (0.98, 1.20)	2.7 (75%)	1.23 (1.19, 1.27)	153.1 (56%)	1.19 (1.05, 1.34)	7.8 (57%)

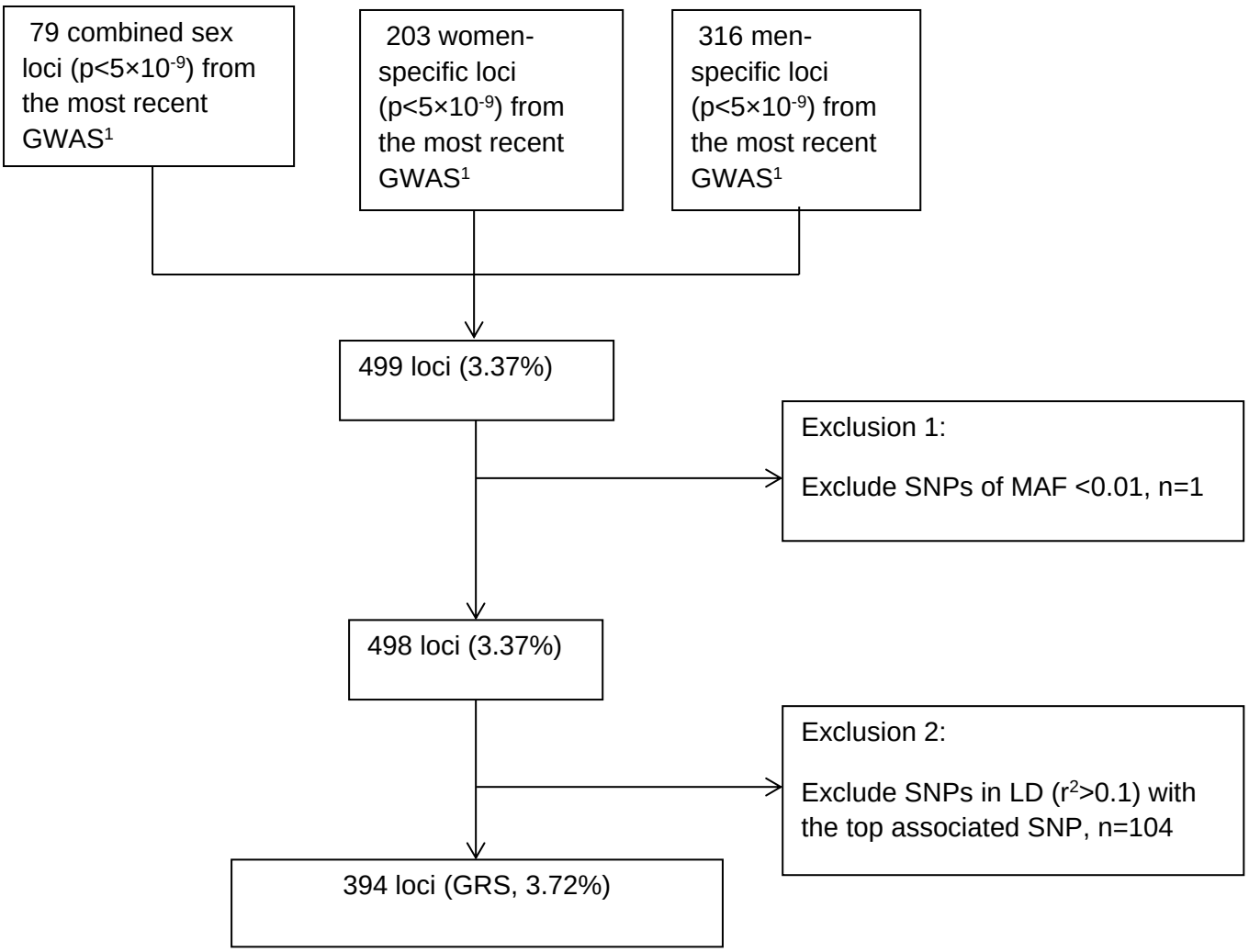
CKD (n=18,034, 6.4%) is defined as long-term renal replacement therapy, $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m² or urinary albumin:creatinine ratio ≥3 mg/mmol.
ORs (95% CI) of any CKD per 0.06 increase in waist-to-hip ratio or per 5 kg/m² increase in BMI are shown. The increment for both adiposity measures equalled 1.10 × measurement-error corrected standard deviation (SD).
† For the conventional analyses, confounders include age, ethnicity, education, region, deprivation index, smoking, physical activity at baseline.
‡ For the genetic analyses, confounder adjusted model was adjusted for top 40 principal components and genotyping array; other models were additionally adjusted for the genetic effects of the adiposity-selected SNPs on reciprocal adiposity (waist-to-hip ratio adjusted for BMI or vice versa), type 2 diabetes, or BP (systolic/diastolic BP).
BMI: body mass index; BP: blood pressure; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

Supplemental table 4: Conventional and genetic associations between adiposity and CKD, by diabetes status with and without adjustment for blood pressure

Population	Definition	CKD at baseline	Adjustments	Waist-to-hip ratio (per 0.06 higher level)				BMI (per 5 kg/m^2 higher level)			
				Conventional†		Genetic‡		Conventional†		Genetic‡	
				OR (95% CI)	χ^2 (% reduction)	OR (95% CI)	χ^2 (% reduction)	OR (95% CI)	χ^2 (% reduction)	OR (95% CI)	χ^2 (% reduction)
Baseline diabetes	Self-report or HbA1c ≥6.5%	2,994/14,825 (20.2%)	Confounder adjusted	1.52 (1.41-1.65)	106 (ref)	1.34 (1.10-1.64)	9 (ref)	1.48 (1.40-1.57)	178 (ref)	1.36 (1.18-1.56)	19 (ref)
			+ BP alone	1.51 (1.40-1.64)	101 (4%)	1.31 (1.06-1.62)	6 (28%)	1.46 (1.38-1.55)	163 (8%)	1.29 (1.11-1.50)	11 (43%)
Baseline pre-diabetes	HbA1c ≥5.7 to <6.5%	922/7,691 (12.0%)	Confounder adjusted	1.44 (1.23-1.69)	20 (ref)	1.05 (0.72-1.53)	0.1 (ref)	1.39 (1.27-1.53)	47 (ref)	1.24 (0.95-1.63)	2 (ref)
			+ BP alone	1.39 (1.18-1.63)	16 (20%)	1.09 (0.73-1.64)	0.2 (**)	1.35 (1.23-1.48)	38 (19%)	1.21 (0.90-1.64)	2 (**)
No baseline diabetes	HbA1c <5.7%	14,118/258,712 (5.5%)	Confounder adjusted	1.50 (1.45-1.56)	465 (ref)	1.14 (1.05-1.23)	10 (ref)	1.43 (1.39-1.47)	662 (ref)	1.30 (1.19-1.41)	38 (ref)
			+ BP alone	1.42 (1.37-1.48)	346 (26%)	1.08 (0.99-1.17)	3 (72%)	1.36 (1.32-1.40)	468 (29%)	1.21 (1.10-1.33)	16 (56%)

CKD (18,034, 6.4%) is defined as long-term renal replacement therapy, $eGFR_{cys\text{-}cr}$<60 mL/min/1.73m^2 or urinary albumin:creatinine ratio ≥3 mg/mmol.
ORs (95% CI) of any CKD per 0.06 increase in waist-to-hip ratio or per 5 kg/m^2 increase in BMI are shown. The increment for both adiposity measures equalled 1.10 × measurement-error corrected standard deviation (SD).
† For the conventional analyses, confounders include age, ethnicity, education, region, deprivation index, smoking, physical activity at baseline.
‡ For the genetic analyses, confounder adjusted model was adjusted for top 40 principal components and genotyping array; other models were additionally adjusted for the genetic effects of the adiposity-selected SNPs on BP (systolic/diastolic BP).
BMI: body mass index; BP: blood pressure; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HbA1c: glycosylated hemoglobin; OR: odds ratio.
** % reduction is not given if confounder adjusted χ^2<10.

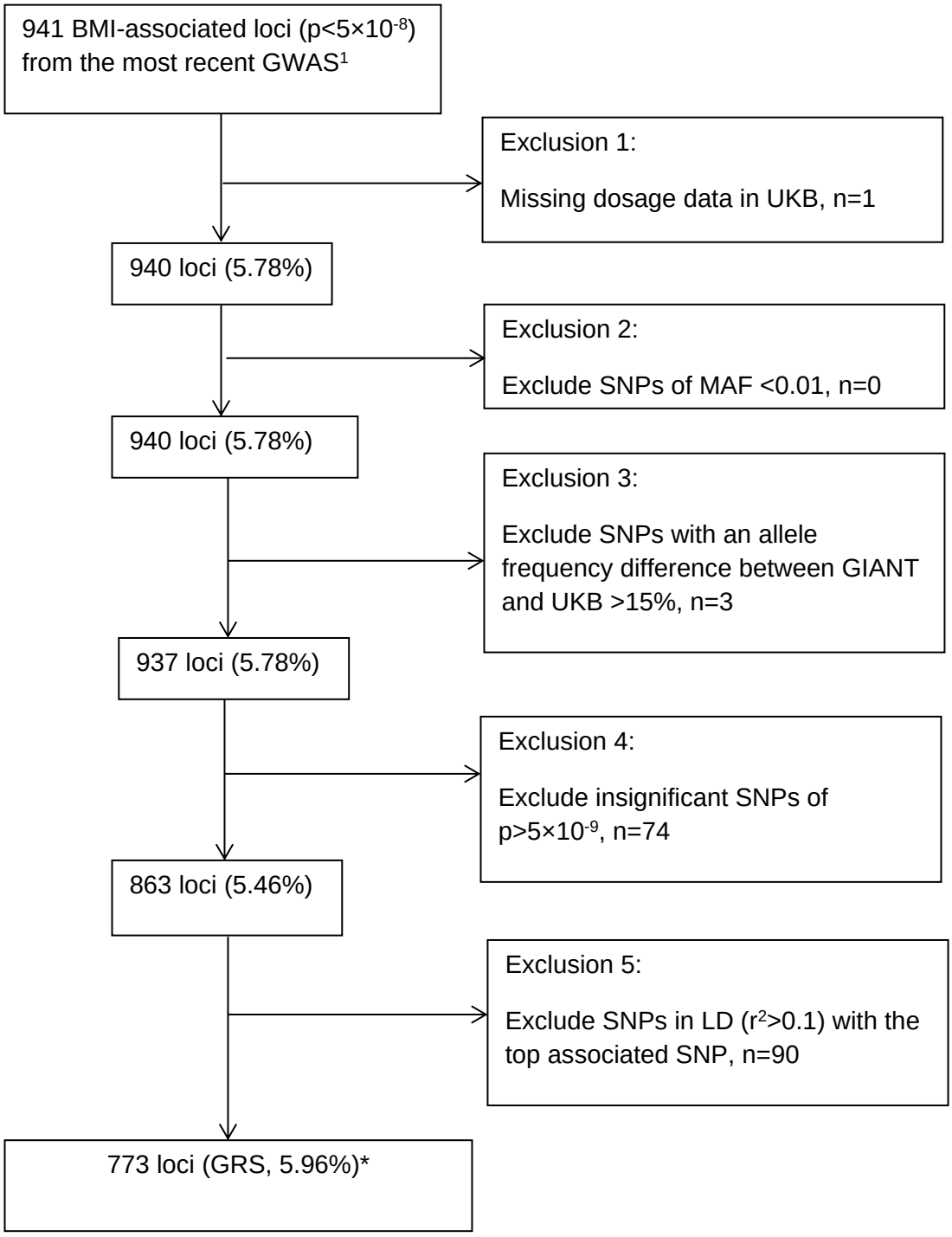
Supplemental figure 1: Selection of variants for the waist-to-hip ratio genetic risk score



GRS: genetic risk score; GWAS: genome-wide association studies; LD: linkage disequilibrium; MAF: minor allele frequency; SNP: single nucleotide polymorphisms.
Variance explained (%) of waist-to-hip ratio in UK Biobank was shown in brackets, the 394 SNPs included in waist-to-hip ratio GRS explained 2.53% and 5.29% of variance in men and women, respectively.
F statistics of GRS was 28.31.
* 115 SNPs of the 394 SNPs were associated with BMI at $p<5\times10^{-9}$.

Reference:
1. Pulit, SL, Stoneman, C, Morris, AP, Wood, AR, Glastonbury, CA, Tyrrell, J, Yengo, L, et al. : Meta-analysis of genome-wide association studies for body fat distribution in 694 649 individuals of European ancestry. Human molecular genetics 28: 166-174, 2019.

Supplemental figure 2: Selection of variants for the BMI genetic risk score

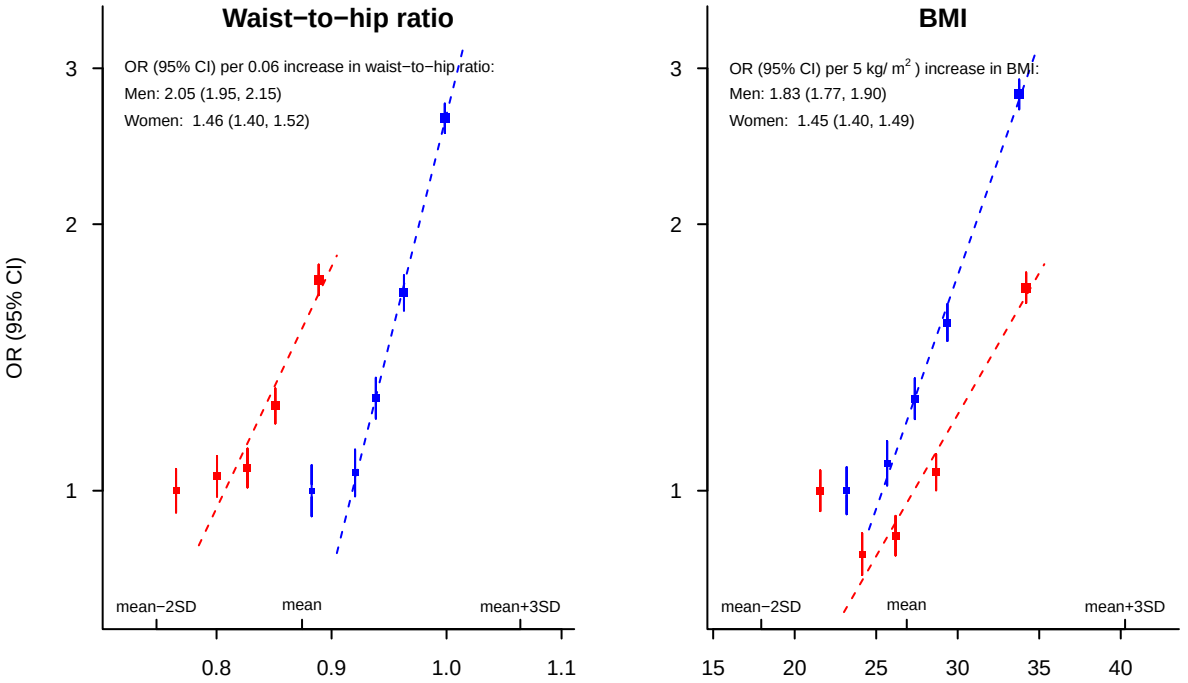


BMI: body mass index; GRS: genetic risk score; GWAS: genome-wide association studies; LD: linkage disequilibrium; MAF: minor allele frequency; SNP: single nucleotide polymorphisms.
Variance explained (%) of BMI in UK Biobank was shown in brackets, the 773 SNPs included in BMI GRS explained 6.14% and 5.54% of variance in men and women, respectively.
F statistics of GRS was 23.63.
* 105 of the 773 SNPs were associated with waist-to-hip ratio at $p<5\times10^{-9}$.

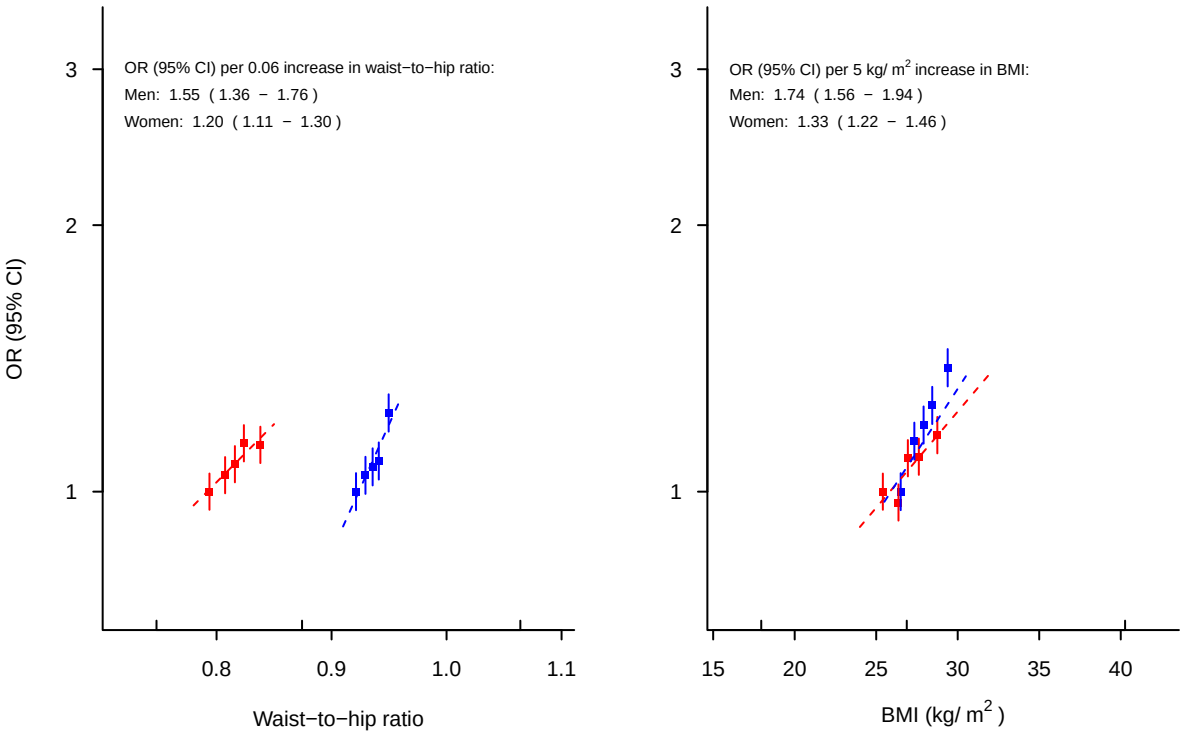
Reference:
1. Yengo, L, Sidorenko, J, Kemper, KE, Zheng, Z, Wood, AR, Weedon, MN, et al.: Meta-analysis of genome-wide association studies for height and body mass index in approximately 700000 individuals of European ancestry. Human molecular genetics 27: 3641-3649, 2018.

Supplemental figure 3: Conventional and genetic associations between adiposity measures and CKD by sex

Conventional analyses



Genetic analyses



CKD (n=18,034, 6.4%) is defined as long−term renal replacement therapy, $eGFR_{cys-cr}$ <60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol.

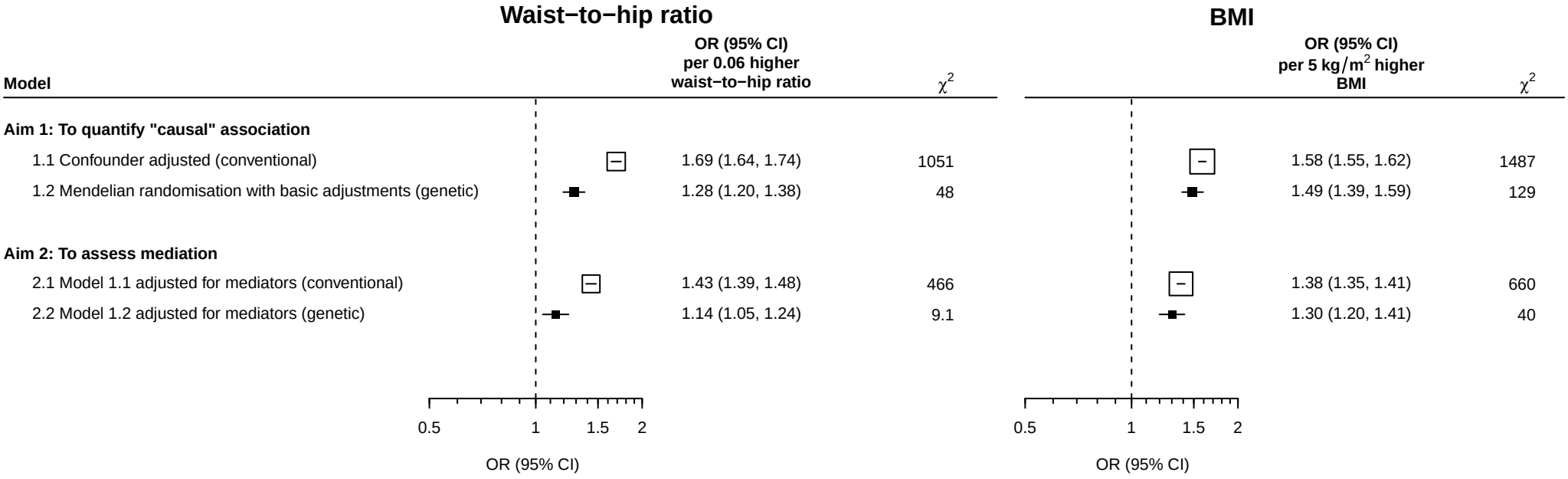
Conventional epidemiological analyses: ORs (95% CI) of any CKD by fifths of measured waist−to−hip ratio and BMI are shown. Model was adjusted for confounders (age, education, region, deprivation index, smoking, physical activity).

Genetic epidemiological analyses: OR (95% CI) of any CKD by fifths of GRS for increasing waist−to−hip ratio and BMI are shown. Model was adjusted for top 40 principal components and genotyping array.

BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; $eGFR_{cys-cr}$: estimated glomerular filtration rate calculated from both serum cystatin C and creatinine.

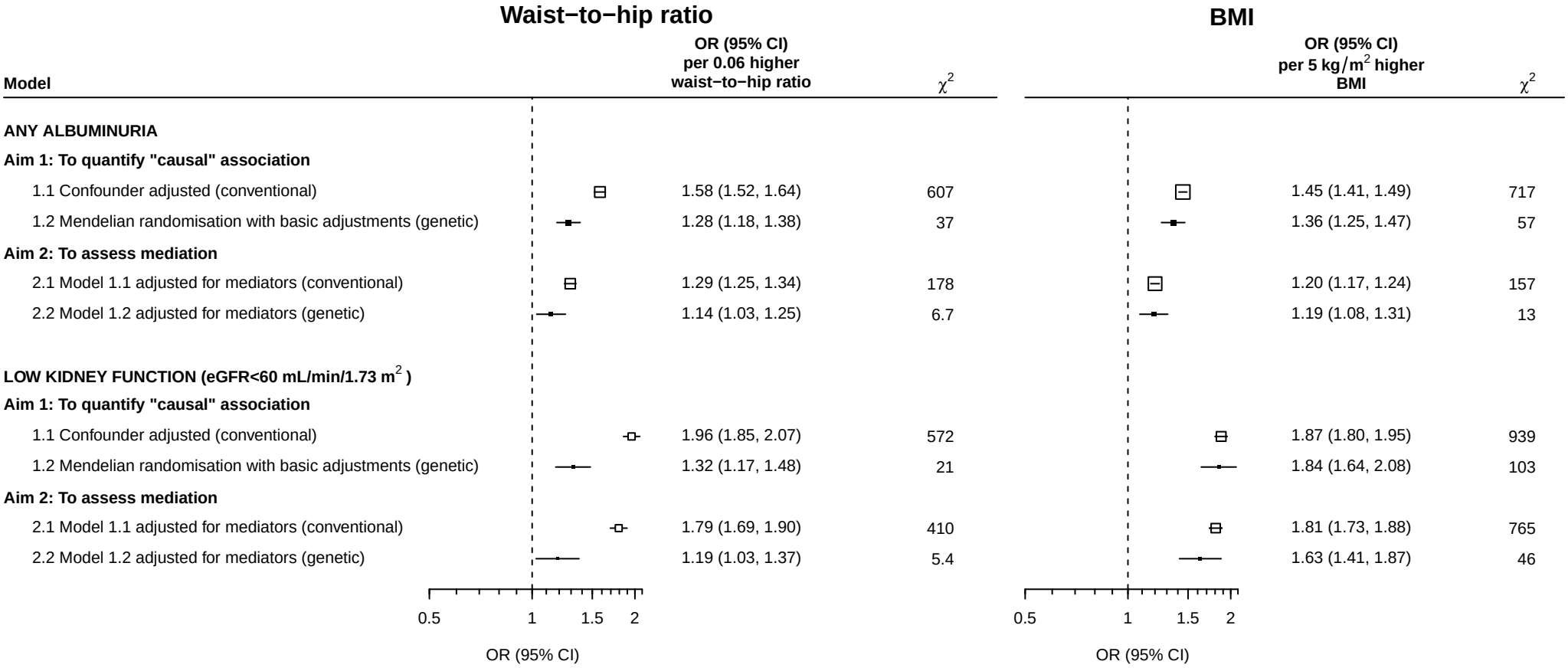
GRS: genetic risk score; OR: odds ratio.

Supplemental figure 4: Conventional and genetic associations between adiposity measures and CKD using GRS with exclusions of loci associated with differential gene expression in kidney



CKD (n=18,034, 6.4%) is defined as long−term renal replacement therapy, $eGFR_{cys-cr}$ <60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol.
ORs (95% CI) of any CKD per 0.06 increase in waist−to−hip ratio or per 5 kg/ m^2 increase in BMI with corrections for measurement error are shown.
Adjustment for mediators were based on measures of baseline diabetes and systolic/diastolic blood pressure in conventional analyses, and the genetic effects of the adiposity−selected SNPs on type 2 diabetes and systolic/diastolic blood pressure in genetic analyses.
BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; $eGFR_{cys-cr}$: estimated glomerular filtration rate calculated from both serum cystatin C and creatinine.
OR: odds ratio; SNP: single nucleotide polymorphism.

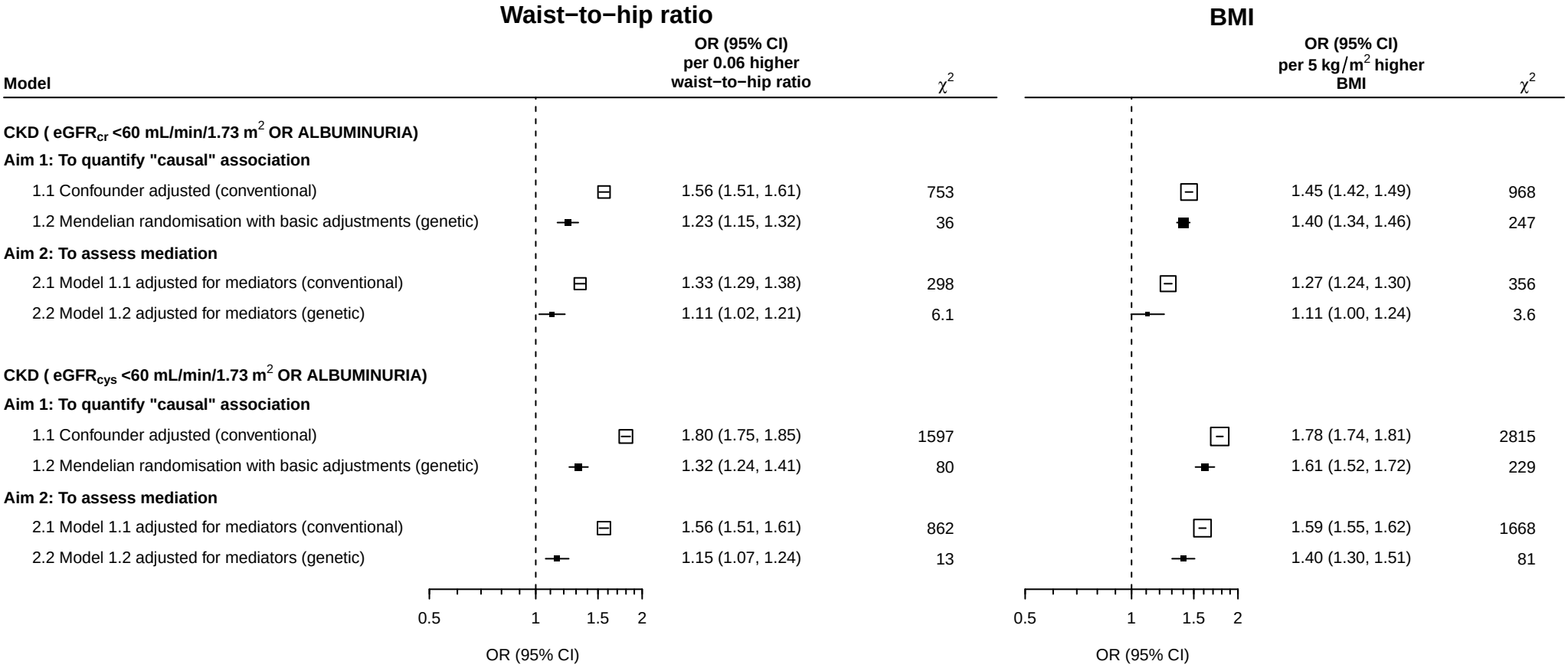
Supplemental figure 5: Conventional and genetic associations between adiposity measures and CKD by different CKD outcomes



Any albuminuria (n=13,413, 4.8%) is defined as urinary albumin:creatinine ratio ≥ 3 mg/mmol.
eGFR<60 mL/min/1.73 m^2 (n=5,812, 2.1%) is defined as long−term renal replacement therapy or $eGFR_{cys-cr}$ <60 mL/min/1.73 m^2 .

OR (95% CI) of any albuminuria per 0.06 increase in waist−to−hip ratio or per 5 kg/ m^2 increase in BMI with corrections for measurement error are shown.
Adjustment for mediators were based on measures of baseline diabetes and systolic/diastolic blood pressure in conventional analyses, and the genetic effects of the adiposity−selected SNPs on type 2 diabetes and systolic/diastolic blood pressure in genetic analyses.
BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; $eGFR_{cys-cr}$: estimated glomerular filtration rate calculated from both serum cystatin C and creatinine.
OR: odds ratio; SNP: single nucleotide polymorphism.

Supplemental figure 6: Conventional and genetic associations between adiposity measures and CKD by eGFR formula

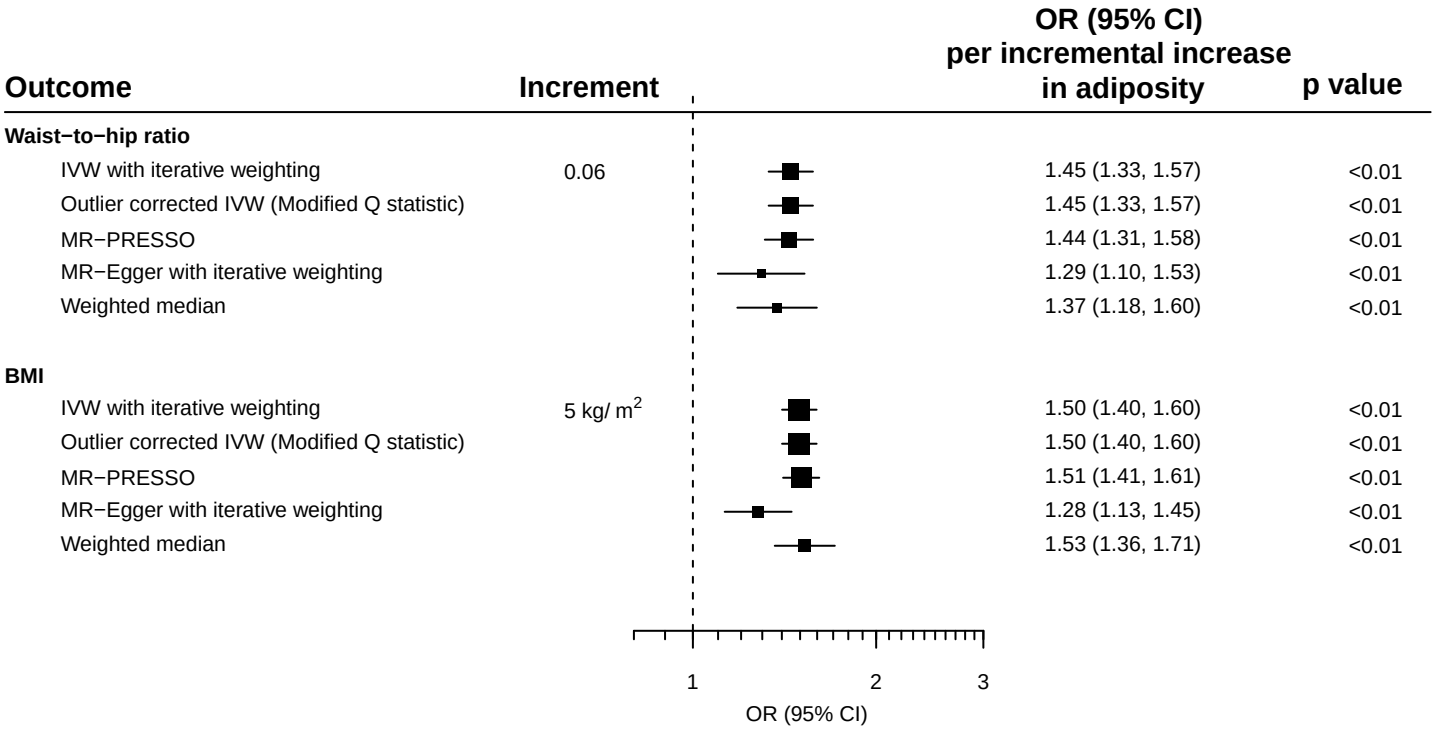


CKD is defined as long−term renal replacement therapy, eGFR<60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol, with 17,987 (6.4%) when $eGFR_{cr}$ used and 22,790 (8.1%) when $eGFR_{cys}$ used.
OR (95% CI) of any CKD per 0.06 increase in waist−to−hip ratio or per 5 kg/ m^2 increase in BMI with corrections for measurement error are shown.

Adjustment for mediators were based on measures of baseline diabetes and systolic/diastolic blood pressure in conventional analyses, and the genetic effects of the adiposity−selected SNPs on type 2 diabetes and systolic/diastolic blood pressure in genetic analyses.

BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease; $eGFR_{cr}$: estimated glomerular filtration rate calculated from serum creatinine.
$eGFR_{cys}$: estimated glomerular filtration rate calculated from serum cystatin C; OR: odds ratio; SNP: single nucleotide polymorphism.

Supplemental figure 7: Genetic associations between adiposity measures and CKD using two−sample Mendelian Randomisation



CKD (n=18,034, 6.4%) is defined as long−term renal replacement therapy, $eGFR_{cys-cr}$ <60 mL/min/1.73 m^2 or urinary albumin:creatinine ratio ≥ 3 mg/mmol.
ORs (95% CI) of any CKD per 0.06 increase in waist−to−hip ratio or per 5 kg/ m^2 increase in BMI using two−sample Mendelian Randomisation methods are shown.
BMI: body mass index; CI: confidence interval; CKD: chronic kidney disease;
$eGFR_{cys-cr}$: estimated glomerular filtration rate calculated from both serum cystatin C and creatinine; OR: odds ratio.