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

Supplemental materials

Supplemental tables

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two-sample Mendelian Randomisation

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

		Fifths of me	asured waist-	to-hip ratio +		Fifth	Fifths of genetic risk score for waist-to-hip ratio ‡					
Characteristics	I	II	III	IV	V	I	II	III	IV	V	(n=132,536)	
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-cr}<60 mL/min/1.73m²or 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%).

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

		Fifths of mea	sured waist-t	o-hip ratio +		Fifths	s of genetic ri	sk score for v	vaist-to-hip ra	atio ‡	Women
Characteristics	I	I	III	IV	V	I	I	III	IV	V	(n=148,692)
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/m²)	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-cr}<60 mL/min/1.73m² 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%).

Supplemental table 2a: Baseline characteristics b	r fifths of measured BMI and genetic risk score (G	RS) in men

		Fifths	of measured	BMI †		Fifths of genetic risk score for BMI ‡					Men
Characteristics	I	II	III	IV	V	I	II	III	IV	V	(n=132,536)
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/m²)	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-cr}<60 mL/min/1.73m² 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%).

		Fifths	of measured	BMI †			Fifths of ge	netic risk sco	re for BMI ‡		Women
Characteristics	I	II	III	IV	V	I	II		IV	V	(n=148,692)
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%)

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

+ 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-cr}<60 mL/min/1.73m² 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%).

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 (p	er 0.06 higher l	evel)	BMI (per 5 kg/m² higher level)					
	Convent	tional †	Gene	Genetic ‡		ional †	Genetic ‡			
Adjustments	OR (95% CI)	χ² (% reduction)	OR (95% CI)	χ² (% reduction)	OR (95% CI)	χ² (% reduction)	OR (95% CI)	χ² (% 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-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 x 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 (p	er 0.06 higher l	evel)	BMI (per 5 kg/m ² higher level)					
	Convent	tional †	Gene	Genetic ‡		tional †	Genetic ‡			
Adjustments	OR (95% CI)	χ² (% reduction)	OR (95% CI)	χ² (% reduction)	OR (95% CI)	χ² (% reduction)	OR (95% CI)	χ² (% 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-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 x 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	Adjustments	Waist-t	o-hip ratio (p	er 0.06 higher	level)	BMI (per 5 kg/m ² higher level)				
		baseline		Conventional†		Gene	tic‡	Conventional†		Genetic‡		
				OR (95% CI)	χ² (%	OR (95% CI)	χ² (%	OR (95% CI)	χ² (%	OR (95% CI)	χ² (%	
					reduction)		reduction)		reduction)		reduction)	
	0.14	0.001/11.005	Confounder	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)	
Baseline	Self-report or 2,994/14, HbA1c >6.5% (20.2%)	2,994/14,825	adjusted									
diabetes HbA1c ≥6.5%	(20.2%)	+ 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%)		
			Confounder	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)	
Baseline pre-	HbA1c ≥5.7 to	922/7,691	adjusted									
diabetes	<6.5%	(12.0%)	+ 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 (**)	
			Confounder	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)	
No baseline diabetes HbA1c <5.7%	14,118/258,712	adjusted										
	⊓DATC <5.7%	(5.5%)	+ 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-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 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<5×10⁻⁹.

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.



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<5×10-9.

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



CKD (n=18,034, 6.4%) is defined as long-term renal replacement therapy, eGFR_{cya-cr} <60 mL/min/1.73 m² or urinary albumin: creatinine ratio \geq 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

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



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

ORs (95% CI) of any CKD per 0.06 increase in waist-to-hip ratio or per 5 kg/ m² increase in BMI 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_{cvs-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

V	Vaist-to-hip	ratio	io BMI					
Model		OR (95% CI) per 0.06 higher waist–to–hip ratio	χ ²		OR (95% CI) per 5 kg/m ² high BMI	her χ^2		
Aim 1: To quantify "causal" association								
1.1 Confounder adjusted (conventional)	. 8	1.58 (1.52, 1.64)	607		1.45 (1.41, 1.49) 717		
1.2 Mendelian randomisation with basic adjustments (genetic)		1.28 (1.18, 1.38)	37		1.36 (1.25, 1.47) 57		
Aim 2: To assess mediation	l I			1				
2.1 Model 1.1 adjusted for mediators (conventional)	¦ =	1.29 (1.25, 1.34)	178		1.20 (1.17, 1.24) 157		
2.2 Model 1.2 adjusted for mediators (genetic)		1.14 (1.03, 1.25)	6.7		1.19 (1.08, 1.31) 13		
LOW KIDNEY FUNCTION (eGFR<60 mL/min/1.73 m ²)				, , , ,				
Aim 1: To quantify "causal" association								
1.1 Confounder adjusted (conventional)	·	1.96 (1.85, 2.07)	572	1	⊟ 1.87 (1.80, 1.95) 939		
1.2 Mendelian randomisation with basic adjustments (genetic)	¦	1.32 (1.17, 1.48)	21	-	1.84 (1.64, 2.08) 103		
Aim 2: To assess mediation	l l			1				
2.1 Model 1.1 adjusted for mediators (conventional)		1.79 (1.69, 1.90)	410		⊕ 1.81 (1.73, 1.88) 765		
2.2 Model 1.2 adjusted for mediators (genetic)		1.19 (1.03, 1.37)	5.4		— 1.63 (1.41, 1.87) 46		
г-т-т-т	• • • • • • • • • • • • • • • • • • • •		r		чтр			
0.5	1 1.5 2		0.	5 1 1.5	2			
OR	(95% CI)			OR (95% CI)				

Any albuminuria (n=13,413, 4.8%) is defined as urinary albumin:creatinine ratio \geq 3 mg/mmol. eGFR<60 mL/min/1.73 m² (n=5,812, 2.1%) is defined as long-term renal replacement therapy or eGFR_{cys-cr} <60 mL/min/1.73 m².

OR (95% CI) of any albuminuria per 0.06 increase in waist-to-hip ratio or per 5 kg/ m² 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

v	/aist-to-hip	ratio			BMI		
Model		OR (95% CI) per 0.06 higher waist-to-hip ratio	χ ²			OR (95% CI) per 5 kg/m ² higher BMI	χ ²
CKD (eGFR _{cr} <60 mL/min/1.73 m ² OR ALBUMINURIA)							
Aim 1: To quantify "causal" association					1		
1.1 Confounder adjusted (conventional)		1.56 (1.51, 1.61)	753			1.45 (1.42, 1.49)	968
1.2 Mendelian randomisation with basic adjustments (genetic)	-	1.23 (1.15, 1.32)	36		-	1.40 (1.34, 1.46)	247
Aim 2: To assess mediation	1 1				1		
2.1 Model 1.1 adjusted for mediators (conventional)		1.33 (1.29, 1.38)	298			1.27 (1.24, 1.30)	356
2.2 Model 1.2 adjusted for mediators (genetic)	- - -	1.11 (1.02, 1.21)	6.1			1.11 (1.00, 1.24)	3.6
CKD (eGFR _{cys} <60 mL/min/1.73 m ² OR ALBUMINURIA)							
Aim 1: To quantify "causal" association							
1.1 Confounder adjusted (conventional)		1.80 (1.75, 1.85)	1597		-	1.78 (1.74, 1.81)	2815
1.2 Mendelian randomisation with basic adjustments (genetic)	+	1.32 (1.24, 1.41)	80			1.61 (1.52, 1.72)	229
Aim 2: To assess mediation	1 1				1		
2.1 Model 1.1 adjusted for mediators (conventional)		1.56 (1.51, 1.61)	862			1.59 (1.55, 1.62)	1668
2.2 Model 1.2 adjusted for mediators (genetic)		1.15 (1.07, 1.24)	13			1.40 (1.30, 1.51)	81
	, <u>, , , , , , , , , , , , , , , , , , </u>			<u> </u>	$\frac{1}{1}$		
0.5	1 1.5 2			0.5	1 1.5 2		
OR	(95% CI)			OR	(95% CI)		

CKD is defined as long-term renal replacement therapy, eGFR<60 mL/min/1.73 m² or urinary albumin:creatinine ratio \geq 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/m² 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

			per in	OR (95% CI) Acremental increa	ise
Outcome	Increment		•	p value	
Waist-to-hip ratio					
IVW with iterative weighting	0.06			1.45 (1.33, 1.57)	<0.01
Outlier corrected IVW (Modified Q statistic)	1			1.45 (1.33, 1.57)	<0.01
MR-PRESSO	1			1.44 (1.31, 1.58)	<0.01
MR–Egger with iterative weighting	1	_		1.29 (1.10, 1.53)	<0.01
Weighted median		_		1.37 (1.18, 1.60)	<0.01
ВМІ					
IVW with iterative weighting	5 kg/ m ²			1.50 (1.40, 1.60)	<0.01
Outlier corrected IVW (Modified Q statistic)	1			1.50 (1.40, 1.60)	<0.01
MR-PRESSO	1	-88-		1.51 (1.41, 1.61)	<0.01
MR–Egger with iterative weighting	1	— — —		1.28 (1.13, 1.45)	<0.01
Weighted median				1.53 (1.36, 1.71)	<0.01
			μιτιτιτη		
	1	2	3		
		OR (95% CI)			

CKD (n=18,034, 6.4%) is defined as long-term renal replacement therapy, $eGFR_{cys-cr} < 60 \text{ mL/min/1.73 m}^2$ or urinary albumin:creatinine ratio $\ge 3 \text{ mg/mmol}$. ORs (95% CI) of any CKD per 0.06 increase in waist-to-hip ratio or per 5 kg/ m² increase in BMI 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.