Causal relevance of obesity on the leading causes of death in women and men: A Mendelian randomization study

Short title: Relevance of obesity to the leading causes of death in women and men

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Abstract

Background

Obesity traits are causally implicated with risk of cardiometabolic diseases. It remains unclear whether there are similar causal effects of obesity traits on other non-communicable diseases. Also, it is largely unexplored whether there are any sex-specific differences in the causal effects of obesity traits on cardiometabolic diseases and other leading causes of death. We therefore tested associations of sex-specific genetic risk scores (GRSs) for body mass index (BMI), waist-hip-ratio (WHR), and WHR adjusted for BMI (WHRadjBMI) with leading causes of mortality, using a Mendelian randomization (MR) framework.

Methods and Findings

We constructed sex-specific GRSs for BMI, WHR, and WHRadjBMI, including 565, 324, and 338 genetic variants, respectively. These GRSs were then used as instrumental variables to assess associations between the obesity traits and leading causes of mortality using an MR design in up to 422,414 participants from the UK Biobank. We also investigated associations with potential mediators and risk factors, including smoking, glycemic and blood pressure traits. Sex-differences were subsequently assessed by Cochran's Q-test (P_{het}).

Up to 227,717 women and 194,697 men with mean (standard deviation) age 56.6 (7.9) and 57.0 (8.1) years, body mass index 27.0 (5.1) and 27.9 (4.2) kg/m^2 and waist-hip-ratio 0.82 (0.07) and 0.94 (0.07), respectively, were included. Mendelian randomization analysis showed that obesity causes coronary artery disease, stroke (particularly ischemic), chronic obstructive pulmonary disease, lung cancer, type 2 and 1 diabetes mellitus, non-alcoholic fatty liver disease, chronic liver disease, and acute and chronic renal failure. A 1 standard deviation higher body mass index led to higher risk of type 2 diabetes in women (OR 3.81; 95% CI 3.42-4.25, $P=8.9\times10^{-130}$) than in men (OR 2.78; 95% CI 2.57-3.02, $P=1.0\times10^{-133}$, $P_{het}=5.1\times10^{-6}$). Waist-hip-ratio led to a higher risk of chronic obstructive pulmonary disease ($P_{het}=5.5\times10^{-6}$) and higher risk of chronic renal failure ($P_{het}=1.3\times10^{-4}$) in men than women.

A limitation of MR studies is potential bias if the genetic variants are directly associated with confounders (pleiotropy), but sensitivity analyses such as MR-Egger supported the main findings. Our study was also limited to people of European descent and results may differ in people of other ancestries.

Conclusions

Obesity traits have an etiological role in the majority of the leading global causes of death. Sex differences exist in the effects of obesity traits on risk of type 2 diabetes, chronic obstructive pulmonary disease, and renal failure, which may have implications on public health.

Abbreviations

BMI, Body mass index; CAD: coronary artery disease; CLD, chronic liver disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; FG, fasting glucose; FI, fasting insulin; GIANT, Genetic Investigation of ANthropometric Traits; GRS, genetic risk score; GWAS, genome-wide association study; MAGIC, the Meta-Analyses of Glucose and Insulin-related traits Consortium; MR, Mendelian randomization; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; T1D, type 1 diabetes; T2D, type 2 diabetes; SBP, systolic blood pressure; SD, standard deviation; SNP, single nucleotide polymorphism; WHO, the World Health Organization; WHR, waist-hip-ratio; WHRadjBMI, waist-hip-ratio adjusted for body mass index.

Introduction

It is increasingly evident that obesity negatively impacts human health and the prevalence of obesity is increasing world-wide (1). Obesity and central fat distribution, commonly measured by body mass index (BMI; obesity usually defined as BMI >30 kg/m^2) and waist-hip-ratio (WHR), respectively, have been linked to cardiometabolic diseases and death in observational studies (2–5). However, conventional observational studies can be affected by bias, confounding, and reverse causation, which might lead to erroneous findings. Mendelian randomization (MR) offers an approach to circumvent these issues by using single nucleotide polymorphisms (SNPs) that reliably associate with an exposure as an instrument to test the causal relationship between an exposure and outcome (6). Owing to the nature of genotypes and therefore genetic associations, MR estimates should be less affected by confounding and reverse causation (S1 Supporting Information) (6). Previous studies have found causal relationships between for example higher BMI and WHR adjusted for BMI (WHRadjBMI) and type 2 diabetes (T2D) and coronary artery disease (CAD), mostly using a limited number of previously known obesity-associated SNPs (7–12). However, previous studies have not thoroughly investigated causal sex-specific relationships, nor have they comprehensively investigated the role that obesity traits play in the leading causes of death beyond these cardiometabolic diseases.

Obesity traits differ between women and men—for example, regional obesity prevalence rates often vary between the sexes (13,14), women have higher SNP-based heritability for WHR (15), and >90% of WHRadjBMI-associated SNPs that show evidence of sexual dimorphism have larger effect sizes in women than men (15). Observational studies have indicated that waist-related traits might be more strongly associated with cardiometabolic outcomes in women, although previous studies are inconclusive (16–20). Only a few studies have investigated sex differences in the effect of genetic risk for obesity-related traits on disease risk (7,10,12). These studies have mostly been restricted to waist-related traits and T2D and CAD, using a limited number of analyses and/or SNPs, but without finding evidence of differences in disease risk between men and women (7,10,12).

A sex difference in the effect of obesity traits on major causes of death could signify that disease burden arising from obesity may be differential in women and men, allowing prioritizing of public

health resources and potentially, sex-specific preventative strategies. We therefore investigated the extent to which obesity traits causally impact the risk of the major global causes of death, and whether relationships with disease are differential between women and men, exploiting recent advances in discovery of obesity-associated SNPs (15).

Methods

Data sources and study participants

The UK Biobank is a prospective UK-based cohort study, with 488,377 genotyped individuals aged 40-69 when recruited (21). UK Biobank has a Research Tissue Bank approval (Research Ethics Committee reference 16/NW/0274, this study's application ID 11867), and all participants gave informed consent.

In the present study, genotype data for up to 422,414 individuals were included, after general genotype and sample quality control procedures, and exclusion of people of non-European ancestry (S1 Supporting Information). Participant characteristics are in Table 1.

Table 1. Characteristics of UK Biobank Participants included in the study.

Characteristic	Men	Women
Individuals, N (%)	194,697 (46.1)	227,717 (53.9)
British, N (%)[a]	173,947 (89.3)	201,278 (88.4)
Age, mean (SD), years	57.0 (8.1)	56.6 (7.9)
UK BiLEVE array, N (%)[b]	23,187 (11.9)	22,755 (10.0)
Body mass index, mean (SD), kg/m2	27.9 (4.2)	27.0 (5.1)
Waist circumference, mean (SD), cm	97.1 (11.3)	84.5 (12.5)
Hip circumference, mean (SD), cm	103.5 (7.6)	103.3 (10.3)
Waist-hip-ratio, mean (SD)	0.94 (0.07)	0.82 (0.07)
Systolic blood pressure, mean (SD), mmHg	144.8 (19.4)	138.0 (21.2)
Diastolic blood pressure, mean (SD), mmHg	86.6 (11.0)	82.3 (11.1)
Type 2 diabetes cases, N (%)	11,768 (6.0)	6,533 (2.9)
Coronary artery disease cases, N (%)	24,430 (12.5)	11,565 (5.1)
Breast cancer cases, N (%)	-	14,294 (6.3)
Chronic liver disease cases, N (%)	822 (0.4)	542 (0.2)
Colorectal cancer cases, N (%)	3,145 (1.6)	2,368 (1.0)
COPD cases, N (%)	7,890 (4.1)	6,789 (3.0)
Dementia cases, N (%)	580 (0.3)	448 (0.2)
Infertility cases, N (%)	85 (0.0)	1,588 (0.7)
Lung cancer cases, N (%)	1,473 (0.8)	1,244 (0.5)

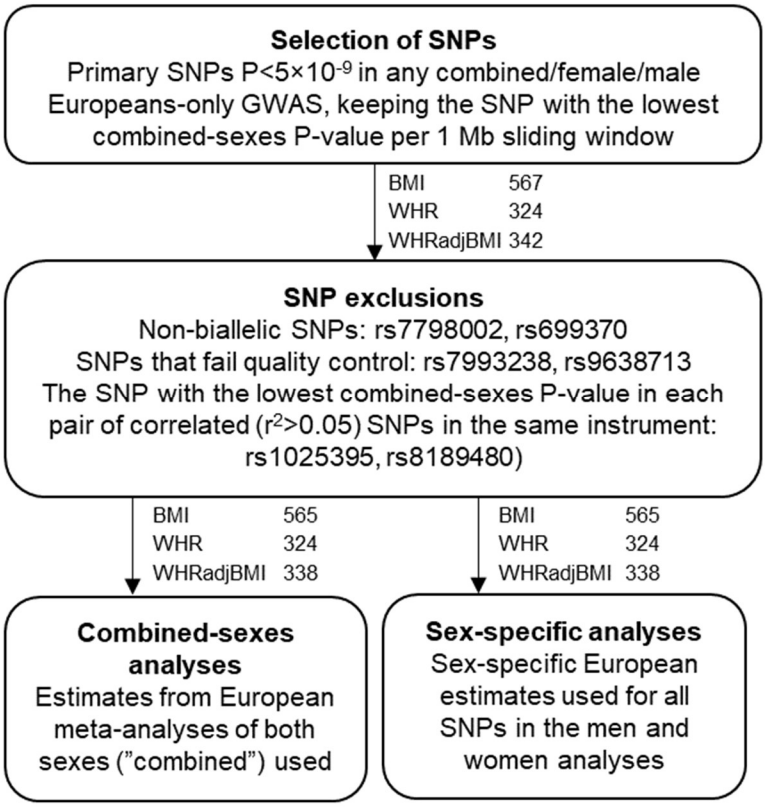
Characteristic	Men	Women
NAFLD cases, N (%)	912 (0.5)	778 (0.3)
Renal failure cases, N (%)	5,704 (2.9)	3,902 (1.7)
Renal failure, acute, cases, N (%)	3,045 (1.6)	1,643 (0.7)
Renal failure, chronic, cases, N (%)	2,581 (1.3)	2,019 (0.9)
Stroke cases, N (%)	6,329 (3.3)	4,437 (1.9)
Stroke, hemorrhagic, cases, N (%)	929 (0.5)	972 (0.4)
Stroke, ischemic, cases, N (%)	2,167 (1.1)	1,177 (0.5)
Type 1 diabetes cases, N (%)	824 (0.4)	675 (0.3)

COPD, chronic obstructive pulmonary disease; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation.
[a]Participants were denoted as "British" if they were in the British ancestry subset as defined by the UK Biobank (21) (based on self-report of British ancestry and similar ancestry according to principal components analysis)
[b]UK BiLEVE array is the number of participants genotyped on that array as opposed to the UK Biobank Axiom array

Instruments

We evaluated several approaches to construct sex-specific genetic risk scores (GRSs) for BMI, WHR, and WHRadjBMI (S1 Supporting Information, Fig A-B in S1 Supporting Information). The approach with the highest ranges of trait variance explained and F-statistics for the relevant obesity trait, and with no demonstrable heterogeneity between men and women, was selected as the main model. In this model, GRSs were constructed by including the primary ("index") genome-wide significant ($P<5\times10^{-9}$) SNPs in the men, women, or combined-sexes analyses in the largest genome-wide association study (GWAS) available with sex-specific European summary statistics, a meta-analysis of the Genetic Investigation of ANthropometric Traits (GIANT) (22,23) and the UK Biobank (Fig 1, S1 Supporting Information) (15). Primary SNPs were identified in the original GWAS (15) by proximal and joint conditional analysis using GCTA in associated loci. Associated loci included all SNPs (associated with the GWAS obesity trait $P<0.05$) ±5 Mb around a top SNP ($P<5\times10^{-9}$) and that were in linkage disequilibrium (LD; $r^2>0.05$) with the top SNP; overlapping loci were merged (15). We then kept the SNP with the lowest combined-sexes P-value within each 1 Mb sliding window to limit correlation between SNPs discovered in different sex-strata in each obesity trait. We excluded non-biallelic SNPs (N=2), SNPs that failed quality control (N=2), and one SNP per pair with long-distance linkage disequilibrium ($r^2>0.05$, N=2) (S1 Supporting Information). For the combined-sexes analyses, SNPs were weighted using estimates from the combined-sexes European meta-analyzed GWASs. For the men- and women-only analyses, SNPs were weighted by their sex-specific European estimates. All

187 SNPs were orientated so that the effect allele corresponded to a higher level of the investigated obesity
188 trait.



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190 **Fig 1. SNP- and weight selection flowchart with number of SNPs for each obesity trait.**
191 SNPs were selected by including the primary ("index") variants for each associated (with SNPs $P<5\times10^{-9}$) locus
192 (assessed for a minimum of ±5 Mb around the top SNP and including all SNPs in linkage disequilibrium
193 $R^2>0.05$ and $P<0.05$, and with primary variants as determined through joint and conditional testing using GCTA
194 in the original study (15)), in any of the men, women, and combined-sexes genome-wide association studies for
195 each obesity trait (15). To further ascertain independence for SNPs selected from different sex-stratified genome-
196 wide association studies and to have the same set of SNPs for all sex-strata, only the SNP with the lowest
197 combined-sexes P-value within each 1 Mb-window was kept. SNPs that were non-biallelic (N=2) or that failed
198 quality control (N=2) were removed, as was one SNP in each pair with long-distance linkage disequilibrium
199 (N=2, using a linkage disequilibrium threshold of $r^2<0.05$ and removing the SNP with the highest combined-
200 sexes P-value). All SNPs were then weighted by their sex-specific Europeans estimates for the men- and women
201 analyses, and by the combined-sexes European estimates for the combined-sexes analyses, using estimates from
202 the original genome-wide association study (15). BMI, body mass index; SNP, single nucleotide polymorphism;
203 WHR, waist-hip-ratio; WHRadjBMI, waist-hip-ratio adjusted for body mass index.
204

205 **Outcomes**

206 We investigated associations between three obesity traits (BMI, WHR, and WHRadjBMI) with all
207 non-communicable diseases on the World Health Organization's (WHO) list of leading mortality

causes world-wide and in high-income countries (24); CAD, stroke (including ischemic, hemorrhagic, and of any cause), chronic obstructive pulmonary disease (COPD), dementia, lung cancer, T2D and type 1 diabetes (T1D), colorectal cancer, renal failure (including acute, chronic and of any cause) and breast cancer in women (Table A in S1 Supporting Information). In addition, we included infertility, non-alcoholic fatty liver disease (NAFLD) and chronic liver disease (CLD) as they have previously been linked to obesity and represent important and increasing burdens of disease (25–31). For T2D and T1D, we drew case definitions from a validated algorithm for prevalent T2D and T1D (using "probable" and "possible" cases) and those the algorithm denoted as "diabetes unlikely" were used as controls (32). For CAD, we used the same case and control definitions as a large GWAS (33). Case and control criteria for the other disease outcomes were defined using self-report data, data from an interview with a trained nurse, and hospital health outcome codes in discussion between two licensed medical practitioners (Table A in S1 Supporting Information). For CAD, acute renal failure, chronic renal failure, stroke of any cause, ischemic stroke and hemorrhagic stroke, exclusions for certain codes were also made in the control groups after defining the case groups.

To assess potential mediation, we also investigated associations between the obesity traits and the potential cardiometabolic risk factors systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting glucose (FG), fasting insulin (FI), and smoking status.

Baseline measurements were used for all continuous traits, including BMI, WHR, WHRadjBMI, SBP and DBP. For SBP and DBP, the mean of the up to two baseline measurements were used. Fifteen mmHg to SBP and 10 mmHg to DBP were added if blood pressure lowering medications were used (defined as self-reported use of such in data-fields 6153 and 6177), as in previous blood pressure GWASs and as suggested in simulation studies (34,35). These anthropometric and blood pressure measurements were then standardized by rank inverse normal transformation of the residuals after regression of the trait on baseline age, age^2, assessment centre, and, if applicable, sex. This was done separately in the men and women only analyses, but jointly in the combined analyses, after any sample quality exclusions (S1 Supporting Information). WHRadjBMI was generated in a similar manner, but with adjustment for BMI as well, as in the original GWAS (15).

Sex-specific summary-level data for plasma FG (in mmol/L, untransformed, corrected to plasma levels using a correction factor of 1.13 if measured in whole blood in the original GWAS) and serum FI (in pmol/L, ln-transformed) were kindly provided by the Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC) investigators and can be downloaded from https://www.magicinvestigators.org/downloads/ (36). SNPs in chromosome:position format were converted to rsIDs using the file All_20150605.vcf.gz from the National Center for Biotechnology Information (NCBI) (37) (available at ftp://ftp.ncbi.nih.gov/snp/organisms/archive/human_9606_b144_GRCh37p13/VCF/). All SNPs were then updated to dbSNP build 151 using the file RsMergeArch.bcp.gz, also from the NCBI (37) (available at ftp://ftp.ncbi.nlm.nih.gov/snp/organisms/human_9606/database/organism_data/).

Smoking status was defined as self-report of being a current or previous smoker or having smoked or currently smoking (most days or occasionally; any code 1 or 2 in any of the data fields 1239, 1249, and 20116).

Statistical analyses

The GRSs were first assessed if they were robustly associated with their respective obesity traits by computing trait variance explained and the F-statistics (S1 Supporting Information, Table B in S1 Supporting Information).

We explored the associations of sex-specific GRSs with outcomes in the UK Biobank (21). For disease outcomes and smoking status, logistic regression was used while for continuous traits (including evaluation of the GRSs in their respective obesity traits and the blood pressure traits) linear regression was used. Associations of sex-specific GRSs with outcome traits that surpassed our P-value thresholds were taken forward for MR to more formally quantify the effect of the obesity trait on the outcome.

Individual-level MR was performed using the Wald method, with the instrumental variable estimate being the ratio between the outcome and risk factor regressed separately on each GRS (38). Standard errors were adjusted to take the uncertainty in both regressions into account by using the first two

terms of the delta method (39–41). MR regressions of the risk factors on the GRSs was performed in controls only for the binary outcomes.

Adjustments were made for baseline age, age^2, array type, assessment centre, 10 principal components, and sex if applicable, for all traits when in clinical units, and array and 10 principal components if rank inverse normal transformed (where adjustment for age, age^2, assessment centre, and if applicable sex had already been performed in the rank inverse normal transformation of the residuals).

Two-sample MR was performed for the effect of the obesity traits on FG and FI, including the inverse-variance weighted (IVW), MR-Egger, and weighted median methods (42–45).

For the obesity trait-risk factor analyses, the P-value threshold was set at <0.003 (=0.05/15) for the regressions and the MRs, for the total of 15 obesity trait-risk factor combinations investigated in the study. We conducted MRs for all obesity traits with smoking status for completeness, since we performed analyses adjusting for smoking status as a sensitivity analysis. We also performed summary-level MRs for the potential risk factors FG and FI directly, as we only had summary-level data for these traits. For the obesity trait-disease analyses, the P-value thresholds for both the regressions and the MRs were set at <0.001 (=0.05/51) for 51 obesity trait-disease combinations investigated in the study. If a combined-sexes regression analysis identified evidence against the null hypothesis it was taken forward for MR; if a regression analysis identified evidence against the null hypothesis in either men or women, MR was performed in both sexes so sexual heterogeneity could be assessed. Sexual heterogeneity between male and female estimates from the linear and logistic regressions and the MRs was assessed using P-values from Cochran's Q test (46). To facilitate comparisons between the obesity traits and sex-strata, estimates were computed per 1 standard deviation (SD) higher obesity trait.

Sensitivity analyses

We performed several sensitivity analyses to ascertain robustness; we performed (a) analyses adjusting for smoking status and (b) analyses restricted to those of genetically confirmed British ancestry only

(S1 Supporting Information). We also (c) evaluated the robustness of the MR findings by comparing different weighting strategies, including use of unweighted and externally weighted (using weights from the GIANT 2015 studies (22,23)) GRSs, and (d) investigated for pleiotropy and performed more pleiotropy-robust sensitivity analyses (44,45) (S1 Supporting Information). We also (e) performed logistic regressions using the same number of cases and controls in men and women for the disease outcomes and (f) conducted analyses using stricter T2D and T1D case definitions (S1 Supporting Information).

Software

The genotype data was handled PLINK v2.00aLM and PLINK v1.90b3 (47) (S1 Supporting Information). Further data handling was performed in Python 3.5.2 (48) using the packages "pandas" (49) and "numpy" (50), R version 3.4.3 (51) and the package "dplyr" (52), bash version 4.1.2(2) (53) and awk (54). Statistical analyses and plots were performed using R version 3.4.3 (51) and packages "ggplot2" (55), "mada" (56), "dplyr" (52), "gridExtra" (57), "lattice" (58), "grid" (51), "grDevices" (51), "ggpubr" (59), and "MendelianRandomization" (42).

Results

Evaluation of genetic risk scores

The GRSs included 565 SNPs for BMI, 324 for WHR and 338 for WHRadjBMI. Trait variance explained varied between 2.5-7.1% and the F-statistic between 4,941-26,311, depending on trait and sex-stratum (Table B in S1 Supporting Information). After having assessed the associations between GRSs and risk factors and disease outcomes using regression analyses, associations that surpassed correction for multiple testing were taken forward for MR (Table C-E and Fig C in S1 Supporting Information).

Several instruments were positively associated with smoking status and with higher estimates in men than in women for both BMI as well as WHR (BMI: $P_{het}=4.7\times10^{-4}$; WHR: $P_{het}=1.3\times10^{-13}$; WHRadjBMI $P_{het}=0.007$) (Table D in S1 Supporting Information). We therefore ran the individual-level MRs adjusting for smoking status to assess potential mediation.

Mendelian randomization of obesity with disease outcomes: all individuals

Obesity traits were causally implicated with diseases that represent the major causes of death (Fig 2 and 3). All measures of obesity were strongly causally related to risk of CAD (odds ratio (OR) ranging from 1.39 for WHRadjBMI to 1.73 for WHR in the combined analyses per 1-SD higher obesity trait). For stroke, both BMI and WHR conferred higher risk (ORs 1.41 and 1.33, respectively). Strong effects were seen for all obesity traits with T2D (OR range 2.13 to 3.64) and BMI also associated with risk of T1D (OR 1.68). Obesity traits increased the risk of kidney disease, including both acute (ORs 1.55 for WHR and 1.80 for BMI) and chronic (ORs 1.72 for WHR and 1.79 for BMI) renal failure. Measures of obesity also causally impacted on risks of COPD (OR 1.68 for BMI and 1.45 for WHR) and lung cancer (BMI OR 1.34). Adjusting for smoking status resulted in reduced magnitudes of effects for COPD and lung cancer traits, suggesting potential mediation (Table F in S1 Supporting Information). In addition to these endpoints, strong effects were seen for risk of NAFLD (OR range 1.61-2.85) and CLD (ORs 1.62 for BMI and 1.83 for WHR).

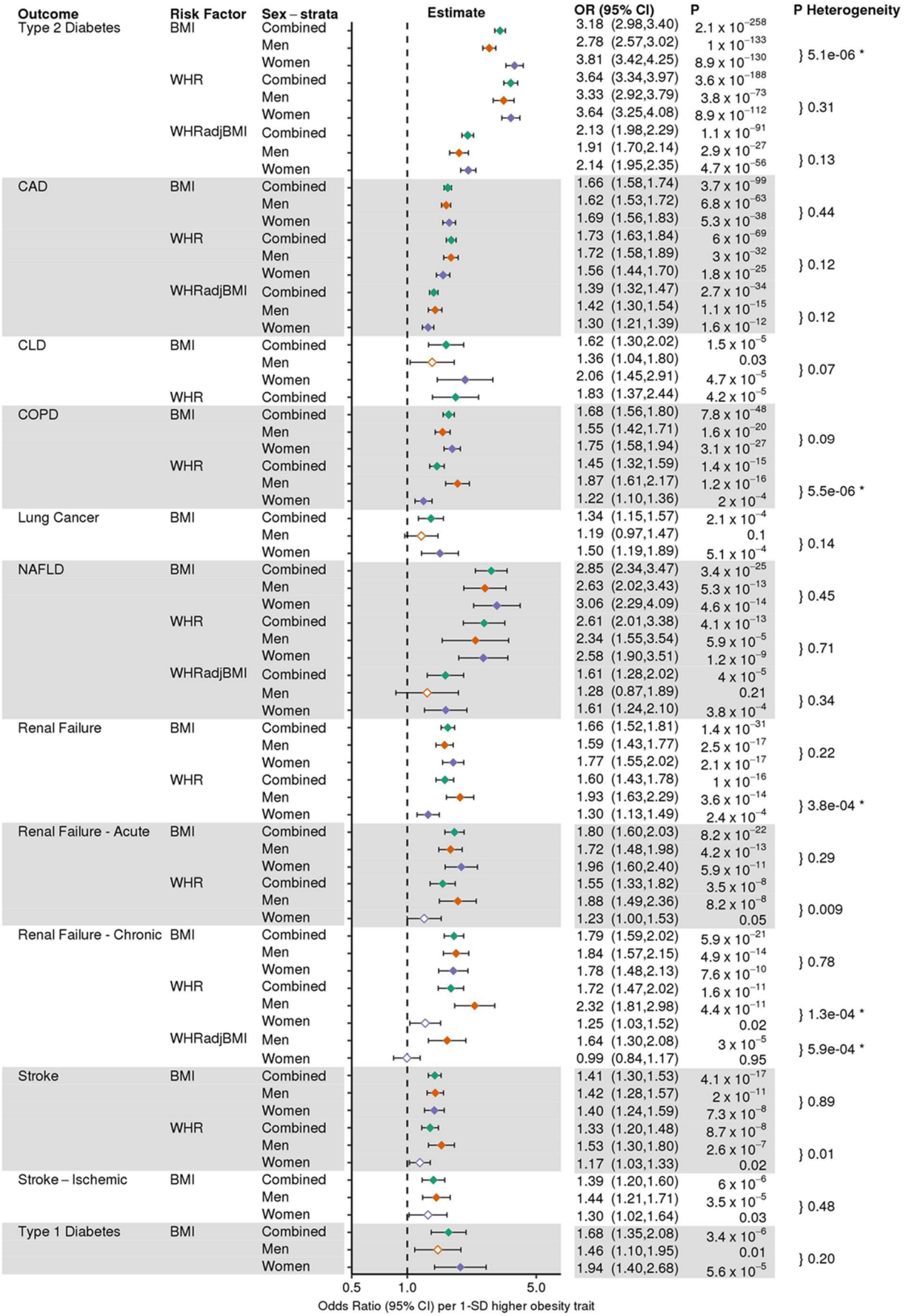
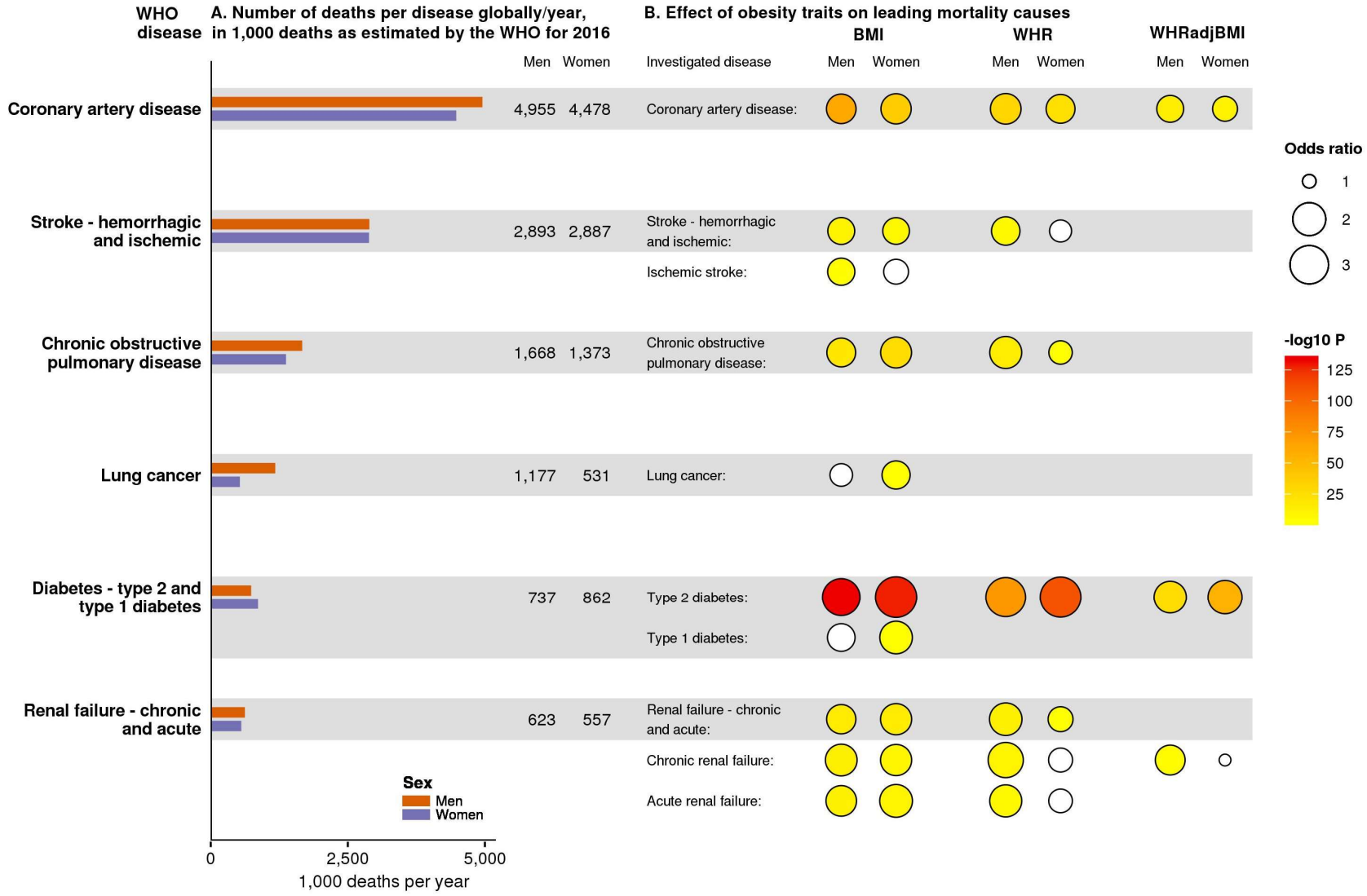


Fig 2. Causal effects of obesity traits on disease outcomes, overall and stratified by sex.
The obesity trait-disease combinations brought forward for Mendelian randomization, with estimates given in odds ratio (95% CI) per 1-SD higher obesity trait. Filled diamonds indicate that the P-value for the obesity trait

to disease endpoint surpasses our threshold for multiple testing; empty diamonds indicate that the P-value does not surpass this threshold (Bonferroni-adjusted P-value-threshold set at <0.001 (=0.05/51) for 51 obesity trait-disease outcome combinations in the study). * denotes that the P-value for heterogeneity (from Cochran's Q test) surpasses our threshold for multiple testing; P_{het}-threshold set at <0.001 (=0.05/48) for 48 male-female comparisons in the study (fewer since breast cancer analyses were performed in women only). ♦, combined-sexes estimates; ♦, male estimates; ♦, female estimates; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; NAFLD, non-alcoholic fatty liver disease; SD standard deviation; WHR, waist-hip-ratio; WHRadjBMI, waist-hip-ratio adjusted for body mass index.



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388 **Fig 3. Overview of the sex-specific effect magnitudes and strengths of association of obesity traits on leading causes of death.**

389 Leading causes of death defined as non-communicable diseases on the WHO top 10 lists of causes of death, globally and in high-income countries, with additional separate

analyses for subclasses of stroke, diabetes, and renal disease. No obesity trait (BMI, WHR, or WHRadjBMI) genetic risk score associated with dementia, colorectal cancer, breast cancer (investigated in women only) or hemorrhagic stroke – these are not shown on the plot. (A) Total number of deaths globally, in 1,000 deaths, as estimated by the WHO for 2016 (60), stratified by sex. For diabetes, estimates for annual number of deaths are for type 1 and type 2 diabetes combined. (B) Obesity trait-disease combinations taken forward for Mendelian randomization showed with circles. Mendelian randomization associations with P-values surpassing our threshold in yellow to red fill depending on P-value (-log10 P-value), white fill indicates a P-value not surpassing our threshold. The size of the circles corresponds to the magnitude of the odds ratio estimate for the Mendelian randomization estimate. Estimates and P-values from the MR analyses of the obesity traits with the disease outcomes using the sex-specific estimates approach. BMI, body mass index; P, P-value; WHR, waist-hip-ratio; WHRadjBMI, waist-hip-ratio adjusted for body mass index; WHO, World Health Organization.

Sensitivity analyses, including restricting analyses to those of genetically confirmed British ancestry only, use of different weighting strategies, analyses using more pleiotropy-robust methods, using the same number of cases and controls in men and women, and use of more stringent diabetes case definitions supported the main findings (S1 Supporting Information, Tables G,H and Fig D-F in S1 Supporting Information).

Mendelian randomization of obesity with disease outcomes: sex-stratified analyses

Five obesity trait-disease associations differed between women and men (Fig 2). The risk of T2D from 1-SD higher BMI was higher in women (OR 3.81; 95% CI 3.42-4.25, $P=8.9\times10^{-130}$) than men (OR 2.78; 95% CI 2.57-3.02, $P=1.0\times10^{-133}$), with strong evidence for sexual heterogeneity ($P_{het}=5.1\times10^{-6}$, P_{het}-threshold set at <0.001 (=0.05/48) for 48 male-female disease estimate comparisons, since breast cancer was investigated in women only). This sexual heterogeneity could also be observed in sensitivity analyses where the number of cases in women and men was similar ($P_{het}=4.4\times10^{-5}$) (Table H in S1 Supporting Information).

WHR increased risk of COPD to a greater extent in men (OR 1.87; 95% CI 1.61-2.17, $P=1.2\times10^{-16}$) than in women (OR 1.22; 95% CI 1.10-1.36, $P=2.0\times10^{-4}$, $P_{het}=5.5\times10^{-6}$), per 1-SD higher WHR. While the association of WHR with smoking was greater in men than in women (Table I in S1 Supporting Information) and estimates of WHR with COPD for both men and women attenuated after adjustment for smoking status, the association of WHR and COPD remained higher in men after adjusting for smoking ($P_{het}=1.2\times10^{-4}$; Table F in S1 Supporting Information).

There was also evidence of WHR leading to a higher risk on renal failure in men than in women. Men had a higher risk of chronic renal failure per 1-SD higher WHR, with the risk in men being OR 2.32

(95% CI 1.81-2.98, P=4.4×10^{-11}) and in women OR 1.25 (95% CI 1.03-1.52, P=0.02, $P_{het}=1.3\times10^{-4}$), with similar sex differences seen for WHRadjBMI. Men also had a higher risk of acute renal failure (men: OR 1.88; 95% CI 1.49-2.36, P=8.2×10^{-8}; women: OR 1.23; 95% CI 1.00-1.53, P=0.05, per 1-SD higher WHR, P_{het}=0.009), although the P_{het}-value did not pass our P_{het}-threshold.

Sensitivity analyses using different GRS weighting strategies strongly supported sex-differences in the effect of BMI on T2D and WHR on chronic renal failure and COPD, but only weakly supported a sex-difference in the effect of WHR on renal failure of any cause (S1 Supporting Information, Fig D,E in S1 Supporting Information).

Potential mechanisms

To identify potential mediators, we assessed the relationship of obesity traits with blood pressure (SBP, DBP), glycemic traits (FG, FI), and smoking status (Tables I-M in S1 Supporting Information). All obesity traits causally impacted risk on SBP, DBP, FG and FI. The increase in DBP arising from elevated BMI was greater in women than men ($P_{het}=3.5\times10^{-5}$, P_{het}-threshold set at <0.003 (=0.05/15) for 15 obesity trait-risk factor combinations). BMI and WHR both associated with higher risk of being a smoker, with the magnitudes of effect being larger in men than women (BMI P_{het}=0.002; WHR $P_{het}=3.7\times10^{-14}$). WHRadjBMI was only associated with smoking status in men.

Discussion

Our study demonstrates that obesity is causally implicated in the etiology of two thirds of the leading causes of death from non-communicable diseases (globally and in high-income countries) (24). Furthermore, we identify that for some diseases, obesity conveys altered magnitudes of risk in men and women. Such sexual dimorphism could be observed in the effects of BMI on T2D and waist-related traits on COPD and renal failure. These findings have potential implications for public health policy.

Obesity traits were causally related to higher risk of T2D, in alignment with previous studies (7–12,20,61). We could not detect a sex difference in risk of T2D from higher WHR or WHRadjBMI. Even though some observational studies have suggested that WHR may be a stronger predictor of T2D

449 risk in women than in men (19,20), studies investigating the effect on T2D risk from genetic
450 predisposition to higher WHRadjBMI have not found evidence of sexual heterogeneity (7,10,12). In
451 contrast, we found that BMI conferred a higher T2D risk in women than in men. Whereas men tend to
452 be diagnosed with T2D at lower BMI than women (62), there may be a stronger association between
453 increase of BMI and T2D risk in women than in men (16,19,61,63–66). Whether this reflects a
454 stronger causal effect of BMI on T2D risk in women has hitherto been unknown. We found no
455 evidence for sexual heterogeneity of the causal effect of BMI on potential glycemic trait risk
456 mediators (FG and FI). There have been indications of higher BMI being observationally associated
457 with lower insulin sensitivity in men than in women, but this observed sex-difference may not reflect a
458 causal pathway or we are not capturing it by our glycemic measurements (67–69). We also found
459 evidence of BMI causally increasing risk of T1D. Previous observational (70) and MR (71) studies
460 have implicated childhood BMI in risk of T1D. As SNPs associated with adult BMI have also been
461 found to affect childhood BMI (71,72), our results may well reflect the consequences of childhood
462 BMI on T1D rather than adult BMI. The results were robust to use of a stricter T1D case definition,
463 minimizing risk of erroneous finding due to misclassification of diabetes type.

464 Higher BMI, WHR and WHRadjBMI increased risk of CAD in both sexes, as shown previously (4,7–
465 9,11,12,16,18). Our obesity trait-CAD analyses did not show evidence for sexual heterogeneity.
466 Observational studies have indicated that waist-related traits may be more strongly associated with
467 cardiovascular disease in women and men, but have not been conclusive (16,18,73). However, a recent
468 study (12) investigated the effect of higher WHRadjBMI, lower gluteofemoral fat distribution, and
469 higher abdominal fat distribution, proxied by genetic variants, on CAD and T2D risk and found no
470 evidence that relationships differed between men and women, similar to our findings. BMI and WHR
471 have previously been observationally associated with risk of stroke (74–76) and a previous MR study
472 found a causal effect of BMI on ischemic stroke (77). However, some studies have found WHR to be
473 an epidemiological risk factor for stroke in men only (74,75). Our results confirm BMI as a causal risk
474 factor for overall stroke in both men and women. In women, the effects of WHR were directionally

consistent with harm, but the estimates were imprecise, probably reflecting insufficient power in the sex-stratified analysis.

Our results also indicate that higher BMI and WHR increase risk of COPD and higher BMI the risk of lung cancer; a likely common mechanism is through smoking. BMI has previously been implicated in COPD, but is not an established epidemiological nor causative risk factor (8,78–80). Obesity may directly contribute to COPD as its diagnosis is partly based on spirometry values, and obesity is associated with lower lung function (80,81). Higher BMI also increased risk of lung cancer in our study, similar to a previous MR study (82). Observational studies tend to identify associations between smoking and lower body weight, but whereas smoking lowers body weight, higher BMI is associated with increased smoking (82–85). We found associations between particularly BMI and WHR with smoking propensity. To assess mediation, we therefore conducted analyses adjusting for smoking status. This attenuated the associations between the obesity markers and risk of COPD and lung cancer, suggesting that smoking status may be on the causal pathway between obesity, COPD and lung cancer. This diminution does not discredit the validity of the MR analyses unadjusted for smoking provided that the obesity instruments only affect smoking propensity through altered obesity (86). Rather, they suggest that higher BMI impacts on disease beyond the immediate physiological effects of obesity: by altering human behavior (i.e. increased smoking, likely motivated as a weight loss strategy (87,88)) and this increased propensity to smoking has additional, far-reaching, deleterious effects on human health, as evidenced by the higher risks of serious lung disease. Higher WHR was associated with higher effects on both COPD and being a smoker in men than in women. Whereas the sex difference in the effect of WHR on COPD persisted after adjustment for smoking status, we cannot rule out that WHR has a higher effect on COPD in men than women through its effect on smoking propensity, but that our smoking phenotype does not fully capture the life-long effects of smoking in men and women.

Our results also provide further evidence for a role of obesity traits in both acute and chronic renal failure using an MR design — previous MR studies assessing these relationships have not been conclusive (7,8,89–91). Obesity may affect chronic renal disease through a number of mechanisms,

including structural changes in the kidney and through higher risks of mediating diseases, such as T2D and renal cell carcinoma (91–95). We found central fat distribution (as measured by WHR and WHRadjBMI) to have higher effects on chronic renal failure in men than in women, with evidence of sexual heterogeneity. The reason for this sex difference is unclear — a recent MR study found both BMI and WHR to increase risk of renal cell carcinoma but with no difference in risk between men and women (95).

Obesity traits associated with increased risk of NAFLD and CLD (important and emerging causes of chronic disease and mortality (27–30)), with the effect on CLD possibly mediated by NAFLD, since CLD may be caused by NAFLD (28). A previous MR study found BMI to increase hepatic triglyceride content (96). Our study confirms a role of both general obesity and central fat distribution in NAFLD and CLD using an MR design. This strengthens evidence of a causal effect and emphasizes the risk of increased CLD burden if the obesity prevalence continues to increase (1,27–30).

Strengths and limitations

Genetic instruments should only affect the outcome through the risk factor of interest and not through any confounders (97,98). We performed sensitivity analyses (MR-Egger, weighted-median based methods) more robust to such bias, which supported the main findings (44,45).

If instruments are weakly associated with their respective traits, it can introduce bias in MR studies (99). We therefore only used instruments strongly associated with their respective risk factor, and performed sensitivity analyses using a variety of SNP-selection and weighting approaches, including unweighted and externally weighted scores, which also supported the main results (41,99,100).

Recent studies have also indicated that there may be slight population stratification in both GIANT and UKBB, although such bias is likely to be minor (101,102). Our study was restricted to individuals of Europeans ancestry; limiting our analyses to those of British ancestry only yielded near-identical results. Associations between the obesity traits and outcomes may differ in other ancestries.

Finally, it is possible that our genetic instrument for WHRadjBMI might show features of collider bias whereby SNPs included in the GRS associate with both higher WHR and lower BMI leading to

potentially spurious findings (103). We note that a recent GWAS (15) evaluated the potential for collider bias in the WHRadjBMI GWAS and found limited evidence for such, although the GRS was associated with higher WHR and lower BMI. The directional consistency of associations between WHR and WHRadjBMI and disease endpoints in our analysis suggests that collider bias is unlikely to represent a major source of error in this study.

Conclusion

Global prevalence of obesity is increasing (1). Our results implicate major obesity traits (BMI, WHR, and WHRadjBMI) in the etiology of the leading causes of death globally, including CAD, stroke, type 2 and 1 diabetes, COPD, lung cancer and renal failure, as well as NAFLD and CLD. The risk increase from obesity traits differs between men and women for T2D, renal failure and COPD. This emphasizes the importance of improved preventative measures and treatment of obesity-related disorders and implies that women and men may experience different disease sequelae from obesity, with potential implications for provision of health services and health policy.

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Supporting Information

S1 Supporting Information.