

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

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

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## 49 **Abstract**

### 50 **Background**

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

### 58 **Methods and Findings**

59 We constructed sex-specific GRSs for BMI, WHR, and WHRadjBMI, including 565, 324, and 338  
60 genetic variants, respectively. These GRSs were then used as instrumental variables to assess  
61 associations between the obesity traits and leading causes of mortality using an MR design in up to  
62 422,414 participants from the UK Biobank. We also investigated associations with potential mediators  
63 and risk factors, including smoking, glycemic and blood pressure traits. Sex-differences were  
64 subsequently assessed by Cochran's Q-test ( $P_{\text{het}}$ ).

65 Up to 227,717 women and 194,697 men with mean (standard deviation) age 56.6 (7.9) and 57.0 (8.1)  
66 years, body mass index 27.0 (5.1) and 27.9 (4.2)  $\text{kg}/\text{m}^2$  and waist-hip-ratio 0.82 (0.07) and 0.94 (0.07),  
67 respectively, were included. Mendelian randomization analysis showed that obesity causes coronary  
68 artery disease, stroke (particularly ischemic), chronic obstructive pulmonary disease, lung cancer, type  
69 2 and 1 diabetes mellitus, non-alcoholic fatty liver disease, chronic liver disease, and acute and chronic  
70 renal failure. A 1 standard deviation higher body mass index led to higher risk of type 2 diabetes in  
71 women (OR 3.81; 95% CI 3.42-4.25,  $P=8.9\times 10^{-130}$ ) than in men (OR 2.78; 95% CI 2.57-3.02,  
72  $P=1.0\times 10^{-133}$ ,  $P_{\text{het}}=5.1\times 10^{-6}$ ). Waist-hip-ratio led to a higher risk of chronic obstructive pulmonary  
73 disease ( $P_{\text{het}}=5.5\times 10^{-6}$ ) and higher risk of chronic renal failure ( $P_{\text{het}}=1.3\times 10^{-4}$ ) in men than women.

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

## 78 **Conclusions**

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

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95 **Abbreviations**

96 BMI, Body mass index; CAD: coronary artery disease; CLD, chronic liver disease; COPD, chronic  
97 obstructive pulmonary disease; DBP, diastolic blood pressure; FG, fasting glucose; FI, fasting insulin;  
98 GIANT, Genetic Investigation of ANthropometric Traits; GRS, genetic risk score; GWAS, genome-  
99 wide association study; MAGIC, the Meta-Analyses of Glucose and Insulin-related traits Consortium;  
100 MR, Mendelian randomization; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; T1D, type  
101 1 diabetes; T2D, type 2 diabetes; SBP, systolic blood pressure; SD, standard deviation; SNP, single  
102 nucleotide polymorphism; WHO, the World Health Organization; WHR, waist-hip-ratio;  
103 WHRadjBMI, waist-hip-ratio adjusted for body mass index.

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## 122 **Introduction**

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

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

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

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

## 153 **Methods**

### 154 **Data sources and study participants**

155 The UK Biobank is a prospective UK-based cohort study, with 488,377 genotyped individuals aged  
156 40-69 when recruited (21). UK Biobank has a Research Tissue Bank approval (Research Ethics  
157 Committee reference 16/NW/0274, this study's application ID 11867), and all participants gave  
158 informed consent.

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

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

<b>Characteristic</b>	<b>Men</b>	<b>Women</b>
Individuals, N (%)	194,697 (46.1)	227,717 (53.9)
British, N (%) <sup>a</sup>	173,947 (89.3)	201,278 (88.4)
Age, mean (SD), years	57.0 (8.1)	56.6 (7.9)
UK BiLEVE array, N (%) <sup>b</sup>	23,187 (11.9)	22,755 (10.0)
Body mass index, mean (SD), kg/m <sup>2</sup>	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)

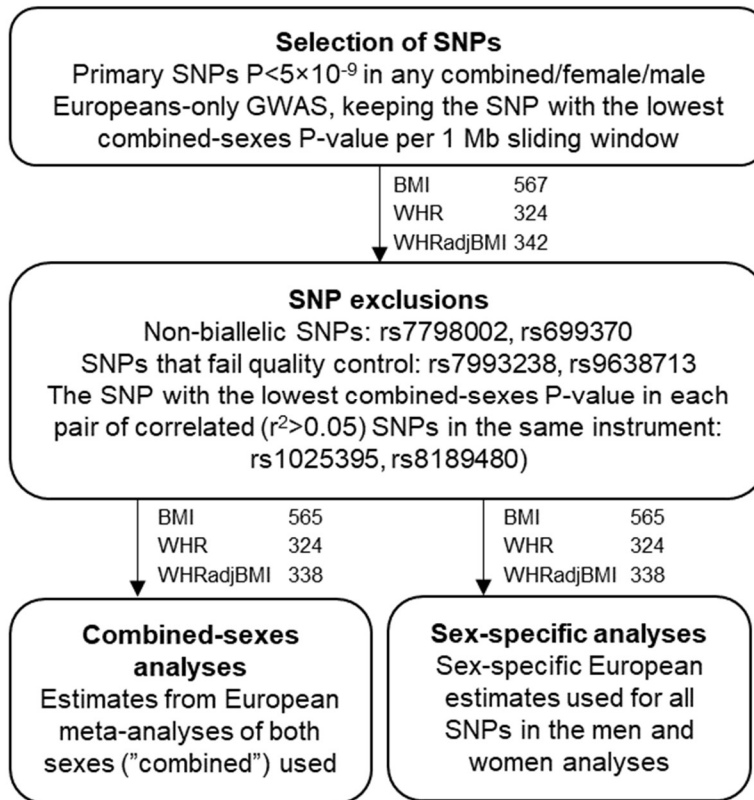
163 COPD, chronic obstructive pulmonary disease; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation.  
164 <sup>a</sup>Participants were denoted as “British” if they were in the British ancestry subset as defined by the UK Biobank (21) (based  
165 on self-report of British ancestry and similar ancestry according to principal components analysis)  
166 <sup>b</sup>UK BiLEVE array is the number of participants genotyped on that array as opposed to the UK Biobank Axiom array  
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## 168 Instruments

169 We evaluated several approaches to construct sex-specific genetic risk scores (GRSs) for BMI, WHR,  
170 and WHRadjBMI (S1 Supporting Information, Fig A-B in S1 Supporting Information). The approach  
171 with the highest ranges of trait variance explained and F-statistics for the relevant obesity trait, and  
172 with no demonstrable heterogeneity between men and women, was selected as the main model. In this  
173 model, GRSs were constructed by including the primary (“index”) genome-wide significant ( $P < 5 \times 10^{-9}$ )  
174 SNPs in the men, women, or combined-sexes analyses in the largest genome-wide association study  
175 (GWAS) available with sex-specific European summary statistics, a meta-analysis of the Genetic  
176 Investigation of ANthropometric Traits (GIANT) (22,23) and the UK Biobank (Fig 1, S1 Supporting  
177 Information) (15). Primary SNPs were identified in the original GWAS (15) by proximal and joint  
178 conditional analysis using GCTA in associated loci. Associated loci included all SNPs (associated  
179 with the GWAS obesity trait  $P < 0.05$ )  $\pm 5$  Mb around a top SNP ( $P < 5 \times 10^{-9}$ ) and that were in linkage  
180 disequilibrium (LD;  $r^2 > 0.05$ ) with the top SNP; overlapping loci were merged (15). We then kept the  
181 SNP with the lowest combined-sexes P-value within each 1 Mb sliding window to limit correlation  
182 between SNPs discovered in different sex-strata in each obesity trait. We excluded non-biallelic SNPs  
183 (N=2), SNPs that failed quality control (N=2), and one SNP per pair with long-distance linkage  
184 disequilibrium ( $r^2 > 0.05$ , N=2) (S1 Supporting Information). For the combined-sexes analyses, SNPs  
185 were weighted using estimates from the combined-sexes European meta-analyzed GWASs. For the  
186 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  $P < 5 \times 10^{-9}$ ) locus  
192 (assessed for a minimum of  $\pm 5$  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 European 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.

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## 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

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

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

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

235 Sex-specific summary-level data for plasma FG (in mmol/L, untransformed, corrected to plasma levels  
236 using a correction factor of 1.13 if measured in whole blood in the original GWAS) and serum FI (in  
237 pmol/L, ln-transformed) were kindly provided by the Meta-Analyses of Glucose and Insulin-related  
238 traits Consortium (MAGIC) investigators and can be downloaded from  
239 <https://www.magicinvestigators.org/downloads/> (36). SNPs in chromosome:position format were  
240 converted to rsIDs using the file All\_20150605.vcf.gz from the National Center for Biotechnology  
241 Information (NCBI) (37) (available at  
242 [ftp://ftp.ncbi.nih.gov/snp/organisms/archive/human\\_9606\\_b144\\_GRCh37p13/VCF/](ftp://ftp.ncbi.nih.gov/snp/organisms/archive/human_9606_b144_GRCh37p13/VCF/)). All SNPs were  
243 then updated to dbSNP build 151 using the file RsMergeArch.bcp.gz, also from the NCBI (37)  
244 (available at [ftp://ftp.ncbi.nlm.nih.gov/snp/organisms/human\\_9606/database/organism\\_data/](ftp://ftp.ncbi.nlm.nih.gov/snp/organisms/human_9606/database/organism_data/)).

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

#### 248 **Statistical analyses**

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

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

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

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

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

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

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

#### 284 **Sensitivity analyses**

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

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

## 294 **Software**

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

## 301 **Results**

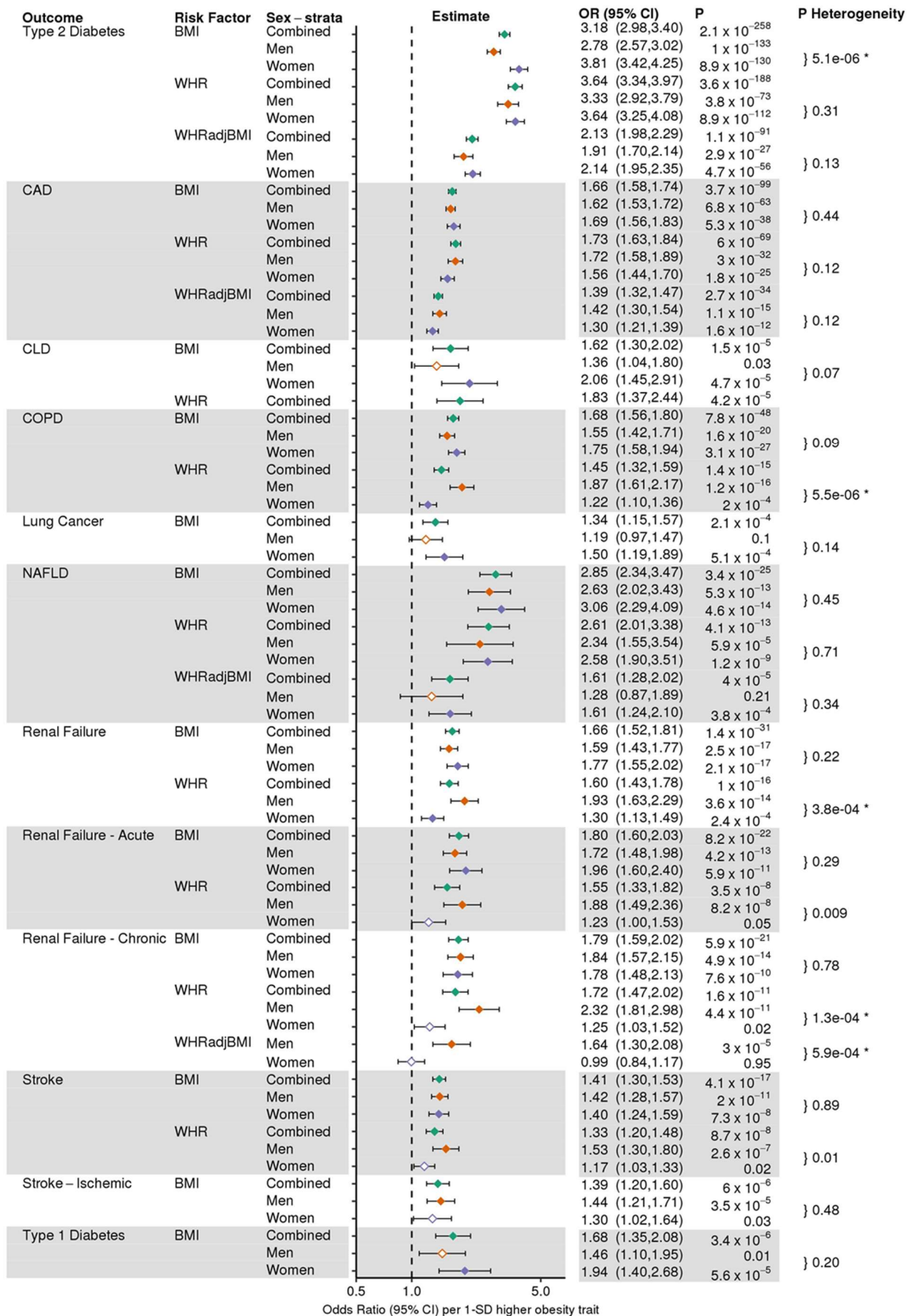
### 302 **Evaluation of genetic risk scores**

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

309 Several instruments were positively associated with smoking status and with higher estimates in men  
310 than in women for both BMI as well as WHR (BMI:  $P_{\text{het}}=4.7\times 10^{-4}$ ; WHR:  $P_{\text{het}}=1.3\times 10^{-13}$ ;  
311 WHRadjBMI  $P_{\text{het}}=0.007$ ) (Table D in S1 Supporting Information). We therefore ran the individual-  
312 level MRs adjusting for smoking status to assess potential mediation.

313 **Mendelian randomization of obesity with disease outcomes: all individuals**

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



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**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

330 to disease endpoint surpasses our threshold for multiple testing; empty diamonds indicate that the P-value does  
331 not surpass this threshold (Bonferroni-adjusted P-value-threshold set at  $<0.001$  ( $=0.05/51$ ) for 51 obesity trait-  
332 disease outcome combinations in the study). \* denotes that the P-value for heterogeneity (from Cochran's Q test)  
333 surpasses our threshold for multiple testing;  $P_{\text{het}}$ -threshold set at  $<0.001$  ( $=0.05/48$ ) for 48 male-female  
334 comparisons in the study (fewer since breast cancer analyses were performed in women only).  $\blacklozenge$ , combined-  
335 sexes estimates;  $\blacklozenge$ , male estimates;  $\blacklozenge$ , female estimates; BMI, body mass index; CAD, coronary artery disease;  
336 COPD, chronic obstructive pulmonary disease; NAFLD, non-alcoholic fatty liver disease; SD standard  
337 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

390 analyses for subclasses of stroke, diabetes, and renal disease. No obesity trait (BMI, WHR, or WHRadjBMI)  
391 genetic risk score associated with dementia, colorectal cancer, breast cancer (investigated in women only) or  
392 hemorrhagic stroke – these are not shown on the plot. (A) Total number of deaths globally, in 1,000 deaths, as  
393 estimated by the WHO for 2016 (60), stratified by sex. For diabetes, estimates for annual number of deaths are  
394 for type 1 and type 2 diabetes combined. (B) Obesity trait-disease combinations taken forward for Mendelian  
395 randomization showed with circles. Mendelian randomization associations with P-values surpassing our  
396 threshold in yellow to red fill depending on P-value ( $-\log_{10}$  P-value), white fill indicates a P-value not  
397 surpassing our threshold. The size of the circles corresponds to the magnitude of the odds ratio estimate for the  
398 Mendelian randomization estimate. Estimates and P-values from the MR analyses of the obesity traits with the  
399 disease outcomes using the sex-specific estimates approach. BMI, body mass index; P, P-value; WHR, waist-  
400 hip-ratio; WHRadjBMI, waist-hip-ratio adjusted for body mass index; WHO, World Health Organization.

401

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

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

408 Five obesity trait-disease associations differed between women and men (Fig 2). The risk of T2D from  
409 1-SD higher BMI was higher in women (OR 3.81; 95% CI 3.42-4.25,  $P=8.9 \times 10^{-130}$ ) than men (OR  
410 2.78; 95% CI 2.57-3.02,  $P=1.0 \times 10^{-133}$ ), with strong evidence for sexual heterogeneity ( $P_{\text{het}}=5.1 \times 10^{-6}$ ,  
411  $P_{\text{het}}$ -threshold set at  $<0.001$  ( $=0.05/48$ ) for 48 male-female disease estimate comparisons, since breast  
412 cancer was investigated in women only). This sexual heterogeneity could also be observed in  
413 sensitivity analyses where the number of cases in women and men was similar ( $P_{\text{het}}=4.4 \times 10^{-5}$ ) (Table  
414 H in S1 Supporting Information).

415 WHR increased risk of COPD to a greater extent in men (OR 1.87; 95% CI 1.61-2.17,  $P=1.2 \times 10^{-16}$ )  
416 than in women (OR 1.22; 95% CI 1.10-1.36,  $P=2.0 \times 10^{-4}$ ,  $P_{\text{het}}=5.5 \times 10^{-6}$ ), per 1-SD higher WHR. While  
417 the association of WHR with smoking was greater in men than in women (Table I in S1 Supporting  
418 Information) and estimates of WHR with COPD for both men and women attenuated after adjustment  
419 for smoking status, the association of WHR and COPD remained higher in men after adjusting for  
420 smoking ( $P_{\text{het}}=1.2 \times 10^{-4}$ ; Table F in S1 Supporting Information).

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

423 (95% CI 1.81-2.98,  $P=4.4\times 10^{-11}$ ) and in women OR 1.25 (95% CI 1.03-1.52,  $P=0.02$ ,  $P_{\text{het}}=1.3\times 10^{-4}$ ),  
424 with similar sex differences seen for WHRadjBMI. Men also had a higher risk of acute renal failure  
425 (men: OR 1.88; 95% CI 1.49-2.36,  $P=8.2\times 10^{-8}$ ; women: OR 1.23; 95% CI 1.00-1.53,  $P=0.05$ , per 1-SD  
426 higher WHR,  $P_{\text{het}}=0.009$ ), although the  $P_{\text{het}}$ -value did not pass our  $P_{\text{het}}$ -threshold.

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

### 431 **Potential mechanisms**

432 To identify potential mediators, we assessed the relationship of obesity traits with blood pressure  
433 (SBP, DBP), glycemic traits (FG, FI), and smoking status (Tables I-M in S1 Supporting Information).  
434 All obesity traits causally impacted risk on SBP, DBP, FG and FI. The increase in DBP arising from  
435 elevated BMI was greater in women than men ( $P_{\text{het}}=3.5\times 10^{-5}$ ,  $P_{\text{het}}$ -threshold set at  $<0.003$  ( $=0.05/15$ )  
436 for 15 obesity trait-risk factor combinations). BMI and WHR both associated with higher risk of being  
437 a smoker, with the magnitudes of effect being larger in men than women (BMI  $P_{\text{het}}=0.002$ ; WHR  
438  $P_{\text{het}}=3.7\times 10^{-14}$ ). WHRadjBMI was only associated with smoking status in men.

### 439 **Discussion**

440 Our study demonstrates that obesity is causally implicated in the etiology of two thirds of the leading  
441 causes of death from non-communicable diseases (globally and in high-income countries) (24).

442 Furthermore, we identify that for some diseases, obesity conveys altered magnitudes of risk in men  
443 and women. Such sexual dimorphism could be observed in the effects of BMI on T2D and waist-  
444 related traits on COPD and renal failure. These findings have potential implications for public health  
445 policy.

446 Obesity traits were causally related to higher risk of T2D, in alignment with previous studies (7–  
447 12,20,61). We could not detect a sex difference in risk of T2D from higher WHR or WHRadjBMI.

448 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 glycaemic 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 glycaemic 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

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

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

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

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

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

#### 514 **Strengths and limitations**

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

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

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

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

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

### 533 **Conclusion**

534 Global prevalence of obesity is increasing (1). Our results implicate major obesity traits (BMI, WHR,  
535 and WHRadjBMI) in the etiology of the leading causes of death globally, including CAD, stroke, type  
536 2 and 1 diabetes, COPD, lung cancer and renal failure, as well as NAFLD and CLD. The risk increase  
537 from obesity traits differs between men and women for T2D, renal failure and COPD. This  
538 emphasizes the importance of improved preventative measures and treatment of obesity-related  
539 disorders and implies that women and men may experience different disease sequelae from obesity,  
540 with potential implications for provision of health services and health policy.

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855 **Supporting Information**

856 **S1 Supporting Information.**