Estimating the causal relationship between smoking and abdominal adiposity using Mendelian randomization

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ABSTRACT

Smokers have on average lower body weight than non-smokers. However, observational studies suggest that, despite a lower body weight, smoking may lead to higher abdominal adiposity. At present, it remains unclear whether this represents a causal relationship, warranting a Mendelian randomization study. Thus, we assessed the causal relationship between smoking and abdominal adiposity using two-sample Mendelian randomization. We used published GWAS results for smoking initiation (n=1,232,091), lifetime smoking (n=462,690) and smoking heaviness (n=337,334) as the exposure traits, and waist-hip ratio (WHR) and waist and hip circumferences (WC and HC) (n up to 697,734), with and without adjustment for body mass index (adjBMI), as the outcome traits. We implemented Mendelian randomization analyses using the recently developed CAUSE and LHC-MR methods that instrument smoking using full GWAS results rather than genome-wide significant loci only. Both CAUSE and LHC-MR indicated a positive causal effect of smoking initiation on WHR (0.13 [95%CI 0.10, 0.16] and 0.49 [0.41, 0.57], respectively) and on WHR_{adjBMI} (0.07 [0.03, 0.10] and 0.31 [0.26, 0.37]). Similarly, they indicated a positive causal effect of lifetime smoking on WHR (0.35 [0.29, 0.41] and 0.44 [0.38, 0.51]) and WHR_{adjBMI} (0.18 [0.13, 0.24] and 0.26 [0.20, 0.31]). The causal estimates for WC_{adjBMI} and HC_{adjBMI} suggested that the higher abdominal fat (i.e. higher WC_{adjBMI}) came at the cost of lower gluteofemoral fat (i.e. lower HC_{adjBMI}). There was no evidence of a causal effect of smoking heaviness on abdominal adiposity. However, we found evidence of reverse causality, where abdominal adiposity increased smoking heaviness. Our findings suggest that smoking initiation and higher lifetime smoking are causally associated with higher abdominal adiposity. Thus, public health efforts aimed at smoking prevention and cessation may also help reduce abdominal adiposity.

INTRODUCTION

Smoking prevention and cessation are critical for public health efforts aiming to reduce the incidence of several common disorders, particularly lung cancer, respiratory disease, and stroke (Hall and Doran, 2016). However, smokers have on average lower body weight than non-smokers, and smoking cessation is associated with weight gain (Sneve and Jorde, 2008, Mackay et al., 2013), which could decrease the success and health benefits of sustained cessation. On the other hand, several studies suggest that, despite a lower body weight, smoking is associated with abdominal adiposity (Albanes et al., 1987, Molarius et al., 1997, Sneve and Jorde, 2008, Terry et al., 2020, Akbartabartoori et al., 2005, Bamia et al., 2004, Canoy et al., 2005, Klesges et al., 1998, Rásky et al., 1996, Stice and Martinez, 2005, Lawlor et al., 2006) – a key risk factor for cardiometabolic disease. The results in observational studies may be biased due to confounding and reverse causality. Thus, it remains unclear whether the association between smoking and abdominal adiposity represents a causal relationship, warranting a Mendelian randomization study.

Mendelian randomization limits the bias of observational studies by utilizing genetic variants associated with the exposure trait as instrumental variables. As genetic alleles are randomly allocated at conception, Mendelian randomization is equivalent to a naturally randomized controlled trial. Previous Mendelian randomization studies have examined the causal effect of smoking heaviness on abdominal obesity (Asvold et al., 2014, Morris et al., 2015, Winslow et al., 2015). While two of the studies found no evidence of causal association with waist-hip ratio (WHR), the third and largest study indicated that there may be a causal association between a higher number of cigarettes per day and higher WHR, even when adjusting for BMI (Morris et al., 2015). However, each of the three studies relied on a single genetic variant for smoking heaviness in the *CHRNA3/5* gene cluster to assess causal relationships, whereas many more smoking-associated loci have been identified in recent studies (Liu et al., 2019). The availability of GWAS summary results of smoking traits with expanded sample sizes allows the use of improved Mendelian randomization methods that utilize multiple genetic instruments to control for pleiotropy and latent heritable confounders, increase statistical power, and assess evidence of bidirectional causal effects (Hemani et al., 2018b, Morrison et al., 2020, Darrous et al., 2021).

Elucidating the causal relationship between smoking and abdominal adiposity is important for public health efforts to prevent and reduce smoking and decrease cardiometabolic risk. Here, we report on Mendelian randomization analyses using the largest GWAS summary-level data of smoking and body fat distribution published to date, to examine the causal effect of smoking initiation, smoking heaviness, and lifetime smoking (which captures smoking heaviness, duration, and time of cessation) on abdominal adiposity.

RESULTS

Effects of smoking initiation and lifetime smoking on abdominal adiposity

In Mendelian randomization analyses by the CAUSE and LHC-MR methods, we found evidence of a positive causal effect of smoking initiation on WHR (0.13 [0.10, 0.16] and 0.49 [0.41, 0.57], respectively) and on WHR_{adjBMI} (0.07 [0.03, 0.10] and 0.31 [0.26, 0.37]). Similarly, we found evidence of a positive causal effect of lifetime smoking on WHR (0.35 [0.29, 0.41] and 0.44 [0.38, 0.51]) and on WHR_{adjBMI} (0.18 [0.13, 0.24] and 0.26 [0.20, 0.31]) (**Figure 1, Supplementary Tables 1-3, Supplementary Figure 1**). Translating to original units, our results imply that ever-smoking causally increases WHR by approximately 0.02 units. For CAUSE, the median shared effect, which reflects the effect induced by correlated horizontal pleiotropy, was zero in all models (**Supplementary Table 1**), indicating there was no bias induced by horizontal pleiotropy. The models also showed low q values (q<0.20) (**Supplementary Table 1**), which indicates a low proportion variants that show correlated horizontal pleiotropy. The LHC-MR results indicated an effect of confounders on WHR and WHR_{adjBMI}, independent of the smoking traits, suggesting the presence of correlated horizontal pleiotropy (**Supplementary Tables 3-4**). However, the reported confounder effect was directionally opposite to the positive causal effects of smoking initiation and lifetime smoking on WHR and WHR_{adjBMI}, suggesting that the confounder effect attenuated the true causal effects.

As WHR is calculated as the ratio of WC and HC, the causal effect of smoking on WHR could be due to an effect on either WC or HC, reflecting the deposition of abdominal fat and gluteofemoral fat, respectively. When we examined the causal effects of smoking initiation and lifetime smoking on WC using the CAUSE and LHC-MR methods, we found evidence of a positive causal effect of smoking initiation on WC (0.12 [0.09, 0.16] and 0.37 [0.14, 0.6], respectively) and on WC_{adjBMI} (0.03 [-0.04, 0.11] and 0.07 [0.03, 0.11]), as well as evidence of a positive causal effect of lifetime smoking on WC (0.35 [95%CI 0.29, 0.41] and 0.42 [0.21, 0.63]) and on WC_{adjBMI} (0.09 [-0.05, 0.23] and 0.02 [-0.03, 0.06]) (**Figure 2, Supplementary Tables 1-4**). While there was also evidence of a positive causal effect of smoking initiation and lifetime smoking on HC (**Figure 2, Supplementary Tables 1-4**), the effect estimates were of lesser magnitude than for WC and changed direction from positive to negative after adjustment for BMI, suggesting that smoking initiation and lifetime smoking led to relatively higher abdominal fat storage at the cost of lower gluteofemoral fat.

Using Mendelian randomization methods that instrument the smoking exposure using genome-wide significant variants only (IVW, MR-Egger, weighted median, weighted mode), the results were largely consistent with those from CAUSE and LHC-MR. In particular, there was evidence of a causal effect of lifetime smoking and smoking initiation on WHR (IVW: 0.18 [95%CI 0.08, 0.28] and 0.07 [0.03, 0.12], respectively) and WHR_{adjBMI} (IVW: 0.18 [0.08, 0.27] and 0.03 [-0.01, 0.07], respectively)

(**Figure 1, Supplementary Tables 5-6, Supplementary Figures 2 and 3**). Similar to CAUSE, the causal estimates for WC_{adjBMI} and HC_{adjBMI} suggested that the higher abdominal fat was at the cost of lower gluteofemoral fat (**Figure 2, Supplementary Tables 5-6, Supplementary Figures 2 and 3**).

There is a considerable genetic correlation between smoking initiation and socioeconomic status (r_g ~ -0.4) (Pasman et al., 2022). To examine whether the causal effects of smoking initiation and lifetime smoking on abdominal adiposity are independent of the genetic effects on socioeconomic status, we performed a multivariable Mendelian randomization analysis. We found that smoking initiation and lifetime smoking are causally associated with WHR, WHR_{adjBMI}, WC and WC_{adjBMI}, even after controlling for the genetic effects on education (**Supplementary Note, Supplementary 7-8**). Thus, our findings suggest that the causal effects of smoking initiation and lifetime smoking on abdominal fat distribution are independent of the genetic effects on socioeconomic status.

Effect of smoking heaviness on abdominal adiposity in past and current smokers

In Mendelian randomization analyses of the association between smoking heaviness and abdominal adiposity, we found no evidence of a causal dose-response relationship between a higher number of cigarettes per day or the cumulative pack years of smoking in adulthood, and abdominal adiposity (**Figure 1-2, Supplementary Tables 1-4**). This suggests that the causal effect of lifetime smoking on abdominal adiposity is not related to the heaviness of smoking per se.

A previous Mendelian randomization study based on a single genetic instrument, the *CHRNA3/5* locus, found that a higher number of cigarettes per day is causally associated with higher WHR in current smokers, even when adjusting for BMI (Morris et al., 2015). To compare, we investigated Wald ratio estimates for the *CHRNA3/5* locus alone, to assess the causal effect of cigarettes per day on abdominal adiposity. Our results were consistent with the previously published findings, suggesting a causal effect of smoking heaviness on WHR_{adjBMI} when instrumenting the exposure using the *CHRNA3/5* locus alone (**Supplementary Table 9**). The lack of evidence of a causal effect when including all currently known variants for smoking heaviness suggests that the previous findings relying on the *CHRNA3/5* locus alone may have been due to a locus-specific pleiotropic effect on smoking heaviness and abdominal adiposity (**Supplementary Figure 4**).

Causal effect of abdominal adiposity on smoking traits

To test whether there was evidence of a causal effect of abdominal adiposity on smoking traits, we used the LHC-MR method to estimate bidirectional causal effects. We found evidence of a positive causal effect of WHR on lifetime smoking (0.08 [0.04, 0.13]), a positive causal effect of WC on smoking initiation (0.12 [0.04, 0.21]) and lifetime smoking (0.14 [0.03, 0.25]), and a positive causal

effect of HC on smoking initiation (0.11 [0.03, 0.2]) and lifetime smoking (0.10 [0.04, 0.16]) (**Figure 3, Supplementary Table 4**). However, each of the causal effects was abolished after adjusting for BMI, suggesting that they may have been due to a causal effect of obesity on smoking, as shown before (Carreras-Torres et al., 2018). However, for smoking heaviness, we found a causal effect of WHR_{adjBMI} on both cigarettes per day (0.24 [0.11, 0.37] and the number of smoking pack years in adulthood (0.07 [0.03, 0.12]), suggesting that abdominal adiposity may be causally associated with heavier smoking, independent of overall adiposity (**Figure 3, Supplementary Table 4**).

DISCUSSION

The present Mendelian randomization analyses suggest that smoking initiation and lifetime smoking are causally associated with abdominal fat distribution, as indicated by higher WHR and WHR_{adjBMI}. The causal estimates for WC and HC suggest that the higher abdominal fat comes at the cost of lower gluteofemoral fat. No evidence of a causal dose-response relationship between the number of pack-years or cigarettes per day and abdominal fat distribution was found, suggesting that the causal associations of smoking with abdominal adiposity are not related to the heaviness of smoking per se. On the other hand, our reverse causal analysis suggested that higher abdominal adiposity may causally increase smoking heaviness.

Our findings are in agreement with several, although not all, cross-sectional observational studies that have shown higher abdominal adiposity in smokers than non-smokers, independent of BMI (Canoy et al., 2005, Clair et al., 2011, Chiolero et al., 2008) (Xu et al., 2007, de Oliveira Fontes Gasperin et al., 2014). While some observational studies have also found that smoking heaviness is associated with abdominal adiposity (Clair et al., 2011, Canoy et al., 2005, Kim et al., 2012), our Mendelian randomization analyses did not show evidence of such relationship. Three previously published Mendelian randomization studies have examined the causal relation between smoking heaviness and abdominal adiposity based on a single variant in the first identified and strongest known locus for smoking heaviness within the *CHRNA3/5* region (Asvold et al., 2014, Morris et al., 2015, Winslow et al., 2015). Of these three studies, the largest study indicated a causal relationship between the number of cigarettes per day and abdominal adiposity, independent of BMI(Morris et al., 2015). When we examined Wald ratio estimates for the *CHRNA3/5* locus alone, we found similar estimates as reported previously towards a causal relationship between smoking heaviness and abdominal fat distribution. The lack of a causal association between smoking heaviness and abdominal fat distribution, when instrumenting smoking heaviness using all currently known loci, suggests that the previous findings based on *CHRNA3/5* alone may have been due to a locus-specific pleiotropic effect (Dudbridge, 2016, Katikireddi et al., 2018, Broms et al., 2012, Schuch et al., 2016).

The causal effects of smoking on body fat distribution may be explained by changes in the circulating levels of cortisol (Direk et al., 2011) and sex-hormones (Ambikairajah et al., 2019). Cortisol levels are higher in smokers than in non-smokers and are associated with increased insulin resistance (Yuen et al., 2013) which is closely connected with abdominal adiposity. Smoking in women has been associated with increased androgen levels and a lower bioavailability of extrogens, which may make female smokers susceptible for developing abdominal adiposity (Brand et al., 2011). In men, smoking has been found to reduce testosterone levels, which is associated with increased abdominal fat deposition in men (Svartberg and Jorde, 2007).

A previous MR study reported that higher BMI has a causal effect on the likelihood of becoming a smoker and the heaviness of smoking (Taylor et al., 2019). Here, we find evidence that there may be a BMI-independent effect of body fat distribution on smoking heaviness: A higher WHR_{adjBMI} or WC_{adjBMI} was causally associated with a higher number of cigarettes smoked per day and a higher number of pack-years smoked in adulthood.

The strengths of the present study are the use of the largest available GWAS summary-level data on smoking and body fat distribution and the application of several complementary MR methods and sensitivity analyses to control for pleiotropic effects, sample overlap, latent heritable confounders, reverse causality and type I error. However, there are also several limitations. First, even if we performed several sensitivity analyses, we cannot completely rule out the possibility of residual pleiotropy on the causal estimates. Second, the sample sizes for body fat distribution in current smokers, which we used to assess the causal relation between smoking heaviness and abdominal adiposity, were relatively small, and thus the statistical power was limited compared to the analyses of smoking initiation and lifetime smoking that included much larger sample sizes. Third, as our population was restricted to European genetic ancestry, the findings may not generalizable to populations of other ancestries.

In conclusion, our results indicate that smoking initiation and higher lifetime smoking causally increase abdominal adiposity, a key risk factor of cardiometabolic disease. Thus, public health efforts for smoking prevention and cessation may provide additional health benefits by helping to reduce abdominal adiposity.

MATERIALS AND METHODS

Mendelian randomization methods

The Causal Analysis Using the Summary Effect estimates (CAUSE) and the Latent Heritable Confounder MR (LHC-MR) methods utilize all genome-wide variants to assess causal estimates rather than genome-wide significant loci only, to improve statistical power and correct for sample

overlap, reduce the chance of type I error, and control for correlated and uncorrelated horizontal pleiotropy (Morrison et al., 2020, Darrous et al., 2021). The CAUSE method assesses the unidirectional causal relationship between an exposure and an outcome trait, by calculating the posterior probabilities of a causal effect and a shared effect, where the causal effect reflects the effect that the variants have on the outcome trait through the exposure, and the shared effect reflects the effect that the variants have on the outcome through confounders (correlated horizontal pleiotropy). The LHC-MR method assesses bidirectional causal relationships by dividing the association between an exposure and an outcome trait into four different effects: the causal effect of the exposure on the outcome, the causal effect of the outcome on the exposure, the effect of confounders that affect the outcome through the exposure (vertical pleiotropy), and the effect of confounders that affect the outcome independently of the exposure (correlated horizontal pleiotropy) (Darrous et al., 2021). More details on the CAUSE and LHC-MR methods are provided in the **Supplementary Note.**

In addition to the CAUSE and LHC-MR methods, we implemented Mendelian randomization using inverse variance weighted, MR-Egger, weighted median, and weighted mode methods, instrumenting the smoking exposure trait using genome-wide significant loci only ($P < 5x10^{-8}$). We only took forward the lead variants that showed a pairwise linkage disequilibrium (LD) $r^2 < 0.001$ and a distance of 10.000kb with all other lead variants associated with the same trait. Variants that were not available in the outcome trait GWAS were substituted by their LD proxies ($r^2 > 0.8$), and ambiguous palindromic variants (A/T, G/C) were excluded. We applied Steiger filtering to remove variants for which the association with the outcome trait was likely to be due to the variant's effect on other traits that influence the outcome trait. We calculated the F statistic to assess the strength of the genetic instruments. The analyses were performed using the TwoSampleMR package in R (Hemani et al., 2018b).

We estimated heterogeneity across the causal estimates of the SNPs using the Meta R package (Schwarzer and Schwarzer). The causal estimates were considered heterogeneous if the P value for Cochran's Q test was significantly different from zero ($P<0.05$) and I^2 was above 25%. We assessed bias introduced by horizontal pleiotropy by implementing the Egger's intercept test. An Egger's intercept that deviated significantly from zero ($P<0.05$) was considered as evidence of horizontal pleiotropy. We used the Rucker framework (Hemani et al., 2018a) to assess whether MR-Egger regression that accounts for horizontal pleiotropy but limits statistical power should be applied instead of the standard inverse variance-weighted model. To visually assess heterogeneity and horizontal pleiotropy, we observed leave-one-out forest plots and funnel plots. To detect individual pleiotropic variants that might bias the results, we used the RadialMR package in R (Bowden et al.,

2018), applying an iterative Cochran's Q method and setting a strict outlier P value threshold of <0.05. The iterative Cochran's Q, either inverse variance-weighted Q or Egger Q, was chosen depending on the Rucker framework results. After removing outlier variants detected with RadialMR, we re-run the Mendelian randomization and sensitivity tests and plots, to make sure that horizontal pleiotropy introduced by the outlier variants had been removed.

Given that previous studies have reported that there is a considerable genetic correlation between smoking status and socioeconomic status (Pasman et al., 2022), we conducted a multivariable Mendelian randomization (MVMR) (Zuber et al., 2020) analysis to assess whether the causal effects of smoking initiation and lifetime smoking on abdominal adiposity remain significant when controlling for the effect of education (n=458,079) (Elsworth et al., 2020). We followed the MVMR steps described previously by Sanderson et al (Sanderson et al., 2019). First, we identified independent, genome-wide significant variants associated with smoking and education ($r^2 < 0.001$ within 10.000kb distance), replacing the variants with proxies ($r^2 > 0.8$) when not available in the outcome trait GWAS. Then, we calculated the conditional mean F-statistic to make sure that the MR relevance assumption is fulfilled, i.e. that the instrumental variable is robustly associated with the exposure trait. We obtained IVW estimates before and after outlier removal for genetic instruments with a mean F statistic > 10, and assessed pleiotropy with conditional Cochran's Q, where P<0.05 was interpreted as evidence of pleiotropy. Further details on the MVMR procedures can be found in the **Supplementary Note**.

Data sources for smoking and body fat distribution

We utilized the largest published GWAS summary level data of European ancestry for smoking initiation (n=1,232,091), defined as whether an individual has ever smoked regularly (yes/no) (Liu et al., 2019); lifetime smoking (n=462,690), which captures the initiation, duration, heaviness, and time since the cessation of smoking (Wootton et al., 2020); and smoking heaviness, defined as cigarettes smoked per day by current smokers only or current and former smokers combined (n=337,334) (Liu et al., 2019), or as the total number of pack-years smoked in adulthood (n = 142,387) (**Supplementary Table 10**).

We also utilized the largest published GWAS summary level data of European ancestry for measures of body fat distribution, including WHR (n=697,734) and WHR adjusted for body mass index (WHR_{adjBMI}, n=694,649) from a meta-analysis of the Genetic Investigation of Anthropometric Traits (GIANT) consortium and the UK Biobank (Pulit et al., 2019); waist and hip circumferences (WC and HC) from the UK Biobank (n=462,166 and n=462,177, respectively); and WC_{adjBMI} and HC_{adjBMI} from

the GIANT consortium (n=231,355 and n=211,117, respectively) (Justice et al., 2017). In the analyses of the causal relation between cigarettes smoked per day and abdominal adiposity in current smokers, we utilized the GIANT consortium results for WHR_{AdjBMI} and WC_{AdjBMI} in current smokers only (n=40,543 and n=43,226, respectively) (Justice et al., 2017). In the Mendelian randomization analyses using the IVW, MR Egger, weighted median and weighted mode methods, which are sensitive to bias when there is a sample overlap between the exposure and outcome traits, we used the GIANT consortium data without the UK Biobank for each of the body fat distribution traits (n between 40,543 and 232,101) (Shungin et al., 2015) (**Supplementary Table 10**).

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Ethics statement

The present study used public GWAS summary level data and did not have direct contact with study participants, thus no ethical approval is needed.

Data availability

The code and curated data for the current analysis are available at https://github.com/MarioGuCBMR/MR_smoking_abdominal_adiposity

Conflicts of interest

The authors report no conflicts of interest.

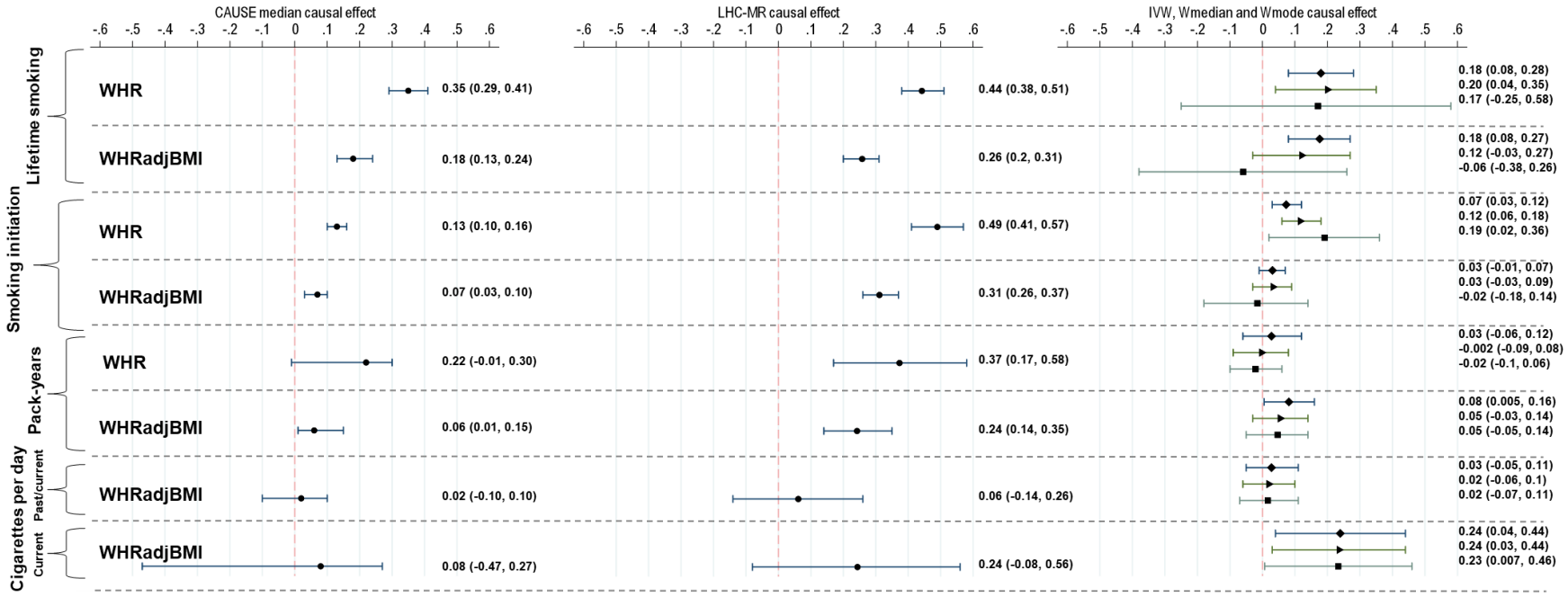

Figure 1: Mendelian randomization results for the association between smoking traits and waist-to-hip ratio (WHR) or waist-to-hip ratio adjusted for body mass index (WHR_{adjBMI}). The results from the CAUSE method are shown in the left panel, the results from the LHC-MR method in the middle panel, and the results from the inverse-variance-weighted (diamond), weighted median (triangle) and weighted mode (square) methods in the right panel.

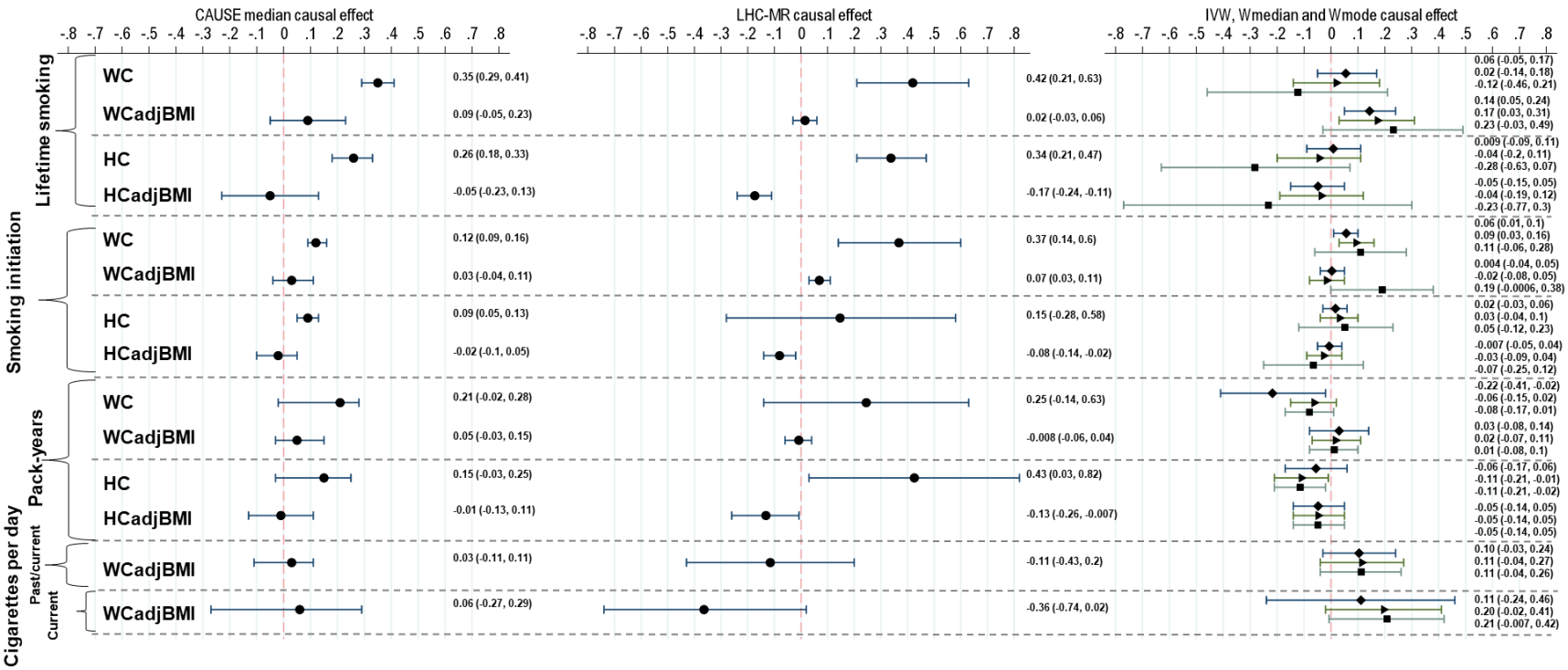

Figure 2: Mendelian randomization results for the association between smoking traits and waist circumference (WC), waist circumference adjusted for body mass index (WC_{adjBMI}), hip circumference (HC), and hip circumference adjusted for body mass index (HC_{adjBMI}). The results from the CAUSE method are shown in the left panel, the results from the LHC-MR method in the middle panel, and the results from the inverse-variance-weighted (diamond), weighted median (triangle) and weighted mode (square) methods in the right panel.

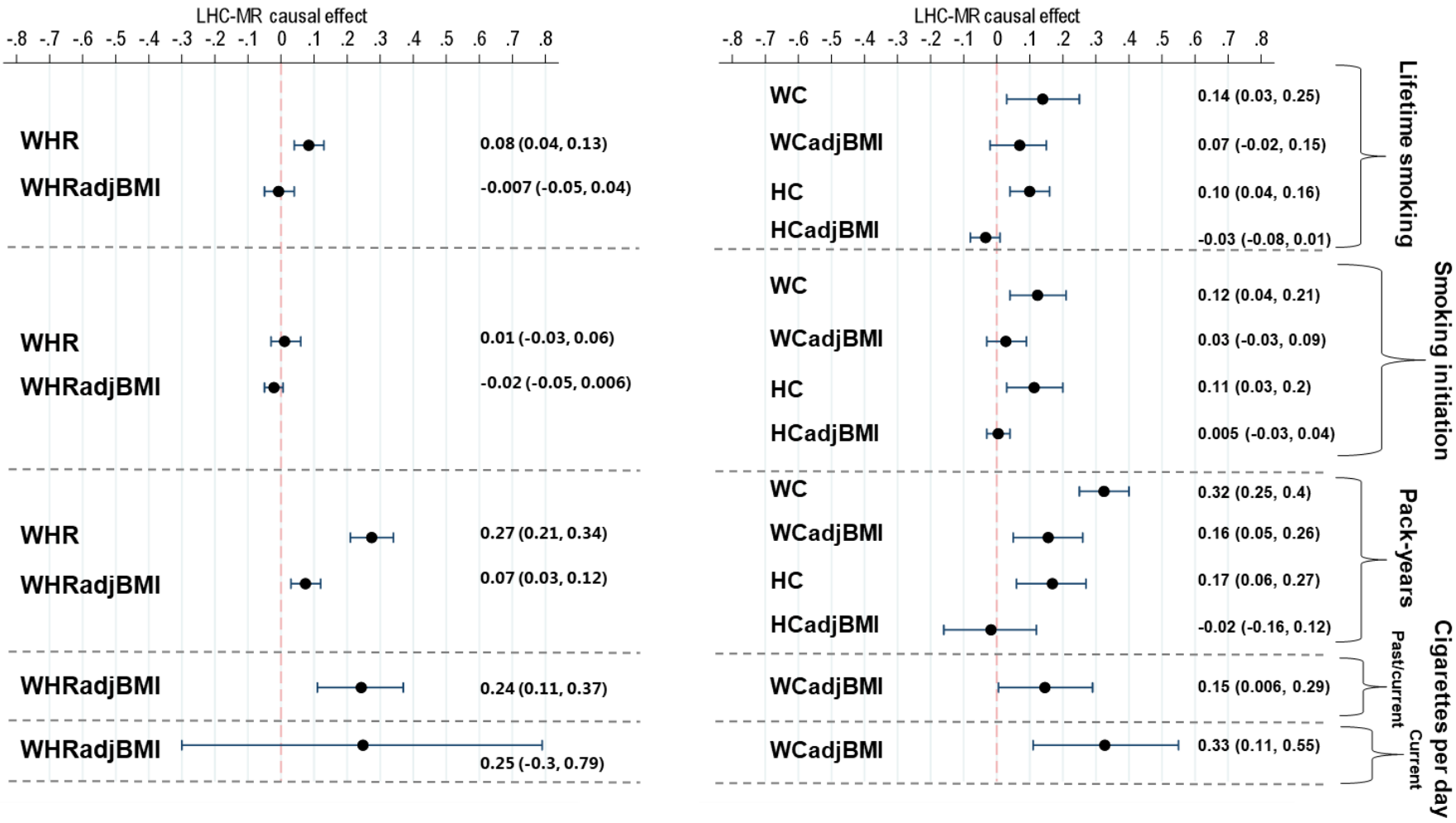

Figure 3. Mendelian randomization results for the causal effect of body fat distribution on smoking traits using the LHC-MR method.

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Supplementary note

Mendelian randomization using the CAUSE Method

We implemented the CAUSE Mendelian randomization analysis applying the following analysis steps, previously described in [1-2]:

1. We merged the exposure and outcome summary statistics using the gwas_merge function of the CAUSE R package [1]. We aligned effect sizes of the variants on the exposure and outcome traits to the same allele.
2. We calculated the nuisance parameters to correct for sample overlap between the exposure and outcome GWAS.
3. We clumped the variants using the LDshrink tool with the 1000 Genomes CEU population data as the reference panel.
4. We assigned the priors for the three model parameters – causal effect, shared effect and q. The priors for the causal effect and the shared effect are automatically set to 0 by CAUSE, while for q, the priors are defined by the user. We set the q priors to qalpha = 1 and qbeta = 2.
5. We calculated two models: the sharing model, where the causal effect is set to 0, and the causal model, where posterior probability for the causal effect is calculated.
6. We compared the causal and shared models against the null and against each other, using the expected log pointwise posterior density (ELPD) method to identify which model was most fitting for the data.

Mendelian randomization using the LHC-MR method

We implemented the LHC-MR Mendelian randomization method [3] using the following parameters:

1. We filtered the GWAS summary data for exposure and outcome traits by excluding variants with imputation quality score INFO < 0.7 or minor allele frequency (MAF) < 0.01.
2. We excluded variants located in the Major Histocompatibility Complex (MHC), present in chromosome 6 between the base pairs 26M and 34M in human genome build 37.
3. We merged the exposure and outcome GWAS summary statistics with two files containing LD information: 1) LD scores for 4,650,107 common high quality variants with imputation quality score >= 0.99 in the UK Biobank GWAS of Neale Lab and MAF > 0.01 in UK10K and UK Biobank; 2) The local LD distribution of the variants.
4. We assigned the starting points for the parameters that LHC-MR will use to run maximum likelihood estimation (MLE). These are: heritability of trait A, heritability of trait B, confounder effect on trait A, confounder effect on trait B, causal effect of A to B, causal effect of B to A, and the intercept of the genetic correlation between A and B.
5. We performed the maximum likelihood estimation.

Mendelian randomization using the inverse variance-weighted (IVW), MR-Egger, weighted median, and weighted mode methods

For the inverse variance-weighted, MR-Egger, weighted median, and weighted mode Mendelian randomization methods, we applied a range of sensitivity tests (**Supplementary Table 6**) and plots (**Supplementary Figure 3**) to assess pleiotropy and ensure that the reported causal effects were unbiased. We considered the results unbiased if they met the following criteria:

1. The causal estimates were considered heterogeneous if the p-value for Cochran's Q test was <0.05 and I^2 was >0.25.
2. Egger's intercept with a p-value <0.05 was considered as evidence that the results are likely to be affected by horizontal pleiotropy. We interpreted the results of Egger's intercept test together with Rucker test results. Rucker test compares Cochran's Q calculated with IVW and MR-Egger causal effects and reports which method is a better fit for the data: If the Cochran's Q is significantly different between IVW and MR-Egger (Rucker test p-value < 0.05), then MR-Egger, which controls for horizontal pleiotropy, is considered to be a better fit for the data.
3. We visualized the effects of heterogeneity and horizontal pleiotropy using leave-one-out forest plots and funnel plots (**Supplementary Figure 3**). If these sensitivity plots showed evidence of outlier variants, we used PhenoScanner [4-5] to examine whether the outlier variants could be possible confounders and were strongly associated with other traits than the smoking-abdominal adiposity relationship.

If the sensitivity tests and plots and PhenoScanner results suggested the presence of horizontal pleiotropy, we implemented the following additional steps:

1. We detected pleiotropic variants using RadialMR's iterative Cochran's Q method (P threshold <0.05). The iterative Cochran's Q, either IVW's Q or Egger's Q', was chosen depending on the result from the Rucker framework test.
2. We excluded any pleiotropic variants and re-implemented the Mendelian Randomization analyses without including these variants. We then reapplied the sensitivity tests and plots to assess whether we had successfully removed the variants introducing horizontal pleiotropy.

Interpretation of the results indicative of causality for inversed variant weighted (IVW), MR-Egger, weighted median, and weighted mode methods:

In the following, we describe the results of the sensitivity analyses and the interpretation of the results of the Mendelian randomization analyses using the IVW, MR-Egger, weighted median, and weighted mode methods.

Lifetime smoking → Abdominal adiposity

The IVW and the weighted median Mendelian randomization methods showed a positive causal association of lifetime smoking with WHR and WC_{adjBMI}. The IVW method also showed a positive causal association of lifetime smoking with WHR_{adjBMI}. (**Figure 1-2 and Supplementary Table 5**). The Cochran's Q test (P > 0.05) and I^2 value (<25%) showed no evidence of heterogeneity between the causal estimates of the instrumental variables. Furthermore, Egger's intercept was not significant and Rucker's test suggested that IVW is a better fit for the data than MR-Egger (**Supplementary Table 5**). However, RadialMR and the sensitivity plots identified five potentially pleiotropic variants for lifetime smoking→WHR_{adjBMI} (rs2867112, rs4543592, rs6778080, rs8078228 and rs889398) and three for lifetime smoking→WC_{adjBMI} (rs1050847, rs17309874 and rs6778080). When checking these variants in PhenoScanner, we did not detect any clear important confounder. Yet, the variant rs6778080 was associated with age at menarche and blood count essay parameters, and rs8078228 with asthma and white cell count.Therefore, for lifetime smoking→WHR_{adjBMI} we report the Mendelian randomization results after removing the five pleiotropic variants. After the extraction of the outliers, the sensitivity tests and sensitivity plots showed no evidence of pleiotropy (**Supplementary Table 6, Supplementary Figure 2 and 3**). Overall, our findings supported a positive causal association between lifetime smoking and WHR, WHR_{adjBMI} and $WC_{adjBMI.}$

Smoking initiation → Abdominal adiposity

The IVW and weighted median Mendelian randomization methods showed a positive causal association of smoking initiation with WHR and WC, and the weighted mode method also showed a positive causal association of smoking initiation with WHR (**Figure 1-2 and Supplementary Table 5**). The Cochran's Q (P > 0.05) and the I^2 value (<25%) did not suggest heterogeneity between the causal estimates of the instrumental variables. Furthermore, Egger's intercept was not significant and Rucker test indicated that IVW was a better fit with the data than MR-Egger (**Supplementary Table 5**). The sensitivity plots identified the variant rs1349979 as a potential pleiotropic variant (**Supplementary Figure 2 and 3)** and PhenoScanner did not detect any potential confounder. Overall, our findings support a positive causal association between smoking initiation and WHR and WC.

Pack-years → Abdominal adiposity

The weighted median and weighted mode Mendelian randomization methods showed a negative causal association of pack-years of smoking with HC. The IVW method showed a positive causal association of pack-years of smoking with WHR_{adjBMI} and a negative causal association with WC. (**Figure 1-2 and Supplementary Table 5**). The Cochran's Q test was not significant (P >= 0.05), whereas the I^2 value showed evidence of heterogeneity (>25%) for pack-years → WC and pack-years → HC. The Egger's intercept was significant and tge Rucker test indicated that the MR-Egger method has a bitter fit with the data than IVW for pack-years → WC and pack-years → HC (**Supplementary Table 5**). The sensitivity plots and RadialMR identified one potentially pleiotropic variant for pack-years → WHR_{adjBMI} (rs10519203) and two variants for pack-years → WC and pack-years → HC (rs136403 and rs150353) (**Supplementary Figure 2 and 3)**. None of the aforementioned pleiotropic variants showed strong associations with potential confounders in PhenoScanner. We reported the Mendelian results for pack-years → WC and pack-years → HC after removing each of the potential pleiotropic variants. After the outlier extraction, the sensitivity tests and sensitivity plots suggested remaining influence of pleiotropy on the results for pack-years → HC (**Supplementary Table 6, Supplementary Figure 2 and 3**). Thus, the Mendelian randomization results do not provide robust support for a causal effect of pack-years of smoking on abdominal adiposity.

Cigarettes per day (past/current) → Abdominal adiposity

None of the Mendelian randomization methods showed a significant causal association of cigarettes per day (past/current) with WHR_{adjBMI} or WC_{adjBMI}, even though each of the methods suggested a positive direction of the causal estimate (**Figure 1-2 and Supplementary Table 5).** The Cochran's Q test (P > 0.05) and I^2 value (<25%) indicated an absence of strong heterogeneity between the causal estimates of the instrumental variables. Furthermore, Egger's intercept was non-significant, and Rucker test indicated that IVW shows a better fit with the data than MR-Egger (**Supplementary Table 5**). The sensitivity plots were consistent with the sensitivity tests (**Supplementary Figure 2 and 3)**. Thus, our findings suggest no causal association between cigarettes per day (past/current) and abdominal adiposity.

Cigarettes per day (current) → Abdominal adiposity

The IVW and weighted median Mendelian randomization methods showed a positive causal association of cigarettes per day (current) with WHR_{adjBMI}. The Cochran's Q test (P > 0.05) and I^2 value (<25%) showed no evidence of heterogeneity between the causal estimates of the instrumental variables. Furthermore, Egger's intercept was non-significant, and Rucker test indicated that IVW is a better with the data than MR-Egger (**Supplementary Table 5**). However, the funnel plot suggested that when removing the rs1317286 variant, the causal effect in the IVW model was

no longer present (**Supplementary Figure 2 and 3)**. To note, rs1317286 represents the strongest known smoking heaviness-locus in CHRNA3/5 and PhenoScanner showed strong associated with smoking heaviness traits. Thus, we further test the locus-specific pleiotropic effects on discrete traits for the variant rs1317286 (Supplementary Figure 4). Thus, our findings suggest that the positive causal association between cigarettes per day (current) and WHR_{adjBMI} may be exclusively driven by the single variant rs1317286.

Multivariable Mendelian randomization using the MVMR package

We used the MVMR package, following the steps previously described in [6], with the exception that we used the function qhet_mvmr that takes pleiotropy into account when estimating the causal effects. Since the ghet_mvmr function is still under development, we also assessed whether pleiotropy may affect the results by manually removing the outliers (step 8 below).

1. We identified independent variants by obtaining genome-wide significant variants for each risk factor, and clumping them using the ld_clump_local function in the package ieugwasr, using the updated European 1000 Genomes reference panel with the following settings: clump_kb = 10000kb and clump_r^2 < 0.001.
2. We replaced the independent lead variants not present in the outcome trait GWAS summary statistics by proxy variants (r^2 > 0.8 in European 1000 Genomes reference panel). To identify the most accurate proxy, we clumped (clump_kb = 10000kb and clump_r^2 < 0.001) all proxies found in the locus of the missing lead variant, using the p-value for the exposure trait for which the missing lead variant was genome-wide significant. If the missing lead variant was found to be genome-wide significant for more than one trait, the p-value of the exposure trait for which the missing variant presented the lowest p-value was used.
3. We harmonized the risk factor and outcome data, so that for each variant, all the genetic effect sizes were aligned to the same allele, while removing palindromic variants.
4. For each SNP, we calculated a covariance matrix using the function phenocov_mvmr(). This function calculates the covariance between the risk factors for each variant using the standard error for each risk factor and the phenotypic correlation between the risk factors in the form of a phenotypic correlation matrix. In this case, the phenotypic correlation between lifetime smoking and education was set to -0.15. The reason for using this correlation cut-off was that the Spearman correlation coefficient in the UK Biobank for “lifetime smoking”, smoking initiation, and packs per year vs. education was -0.1392, -0.0904, and -0.1837, respectively (all with p < 0.00001).
5. We calculated the conditional F-statistic of the set of independent variants with each risk factor. The conditional F-statistic was calculated using the function strength_mvmr that calculates the analog of the F-statistic in a multivariable setting. If the conditional F-statistic for lifetime smoking or for education was < 10, we considered that the set of independent variants was weakly associated with the risk factors.
6. If the conditional F-statistic for all risk factors was > 10, we calculated conditional Cochran’s Q to test whether the causal effect estimated with IVW may be biased due to pleiotropy. We considered a p-value < 0.05 in the conditional Cochran’s Q test as evidence of pleiotropy.
7. We calculated IVW causal effects using the ivw_mvmr() function.
8. To test whether the IVW causal effect may be biased by pleiotropy, we re-implemented steps 4-7 after removing the outlier variants that could introduce pleiotropy. We calculated the conditional Cochran’s Q for each variant and removed variants with Cochran’s Q > 3.84. While this threshold

is stringent and may have removed variants that were not true outliers, we used this to ensure that our results hold without outlier variants.

Supplementary Note References:

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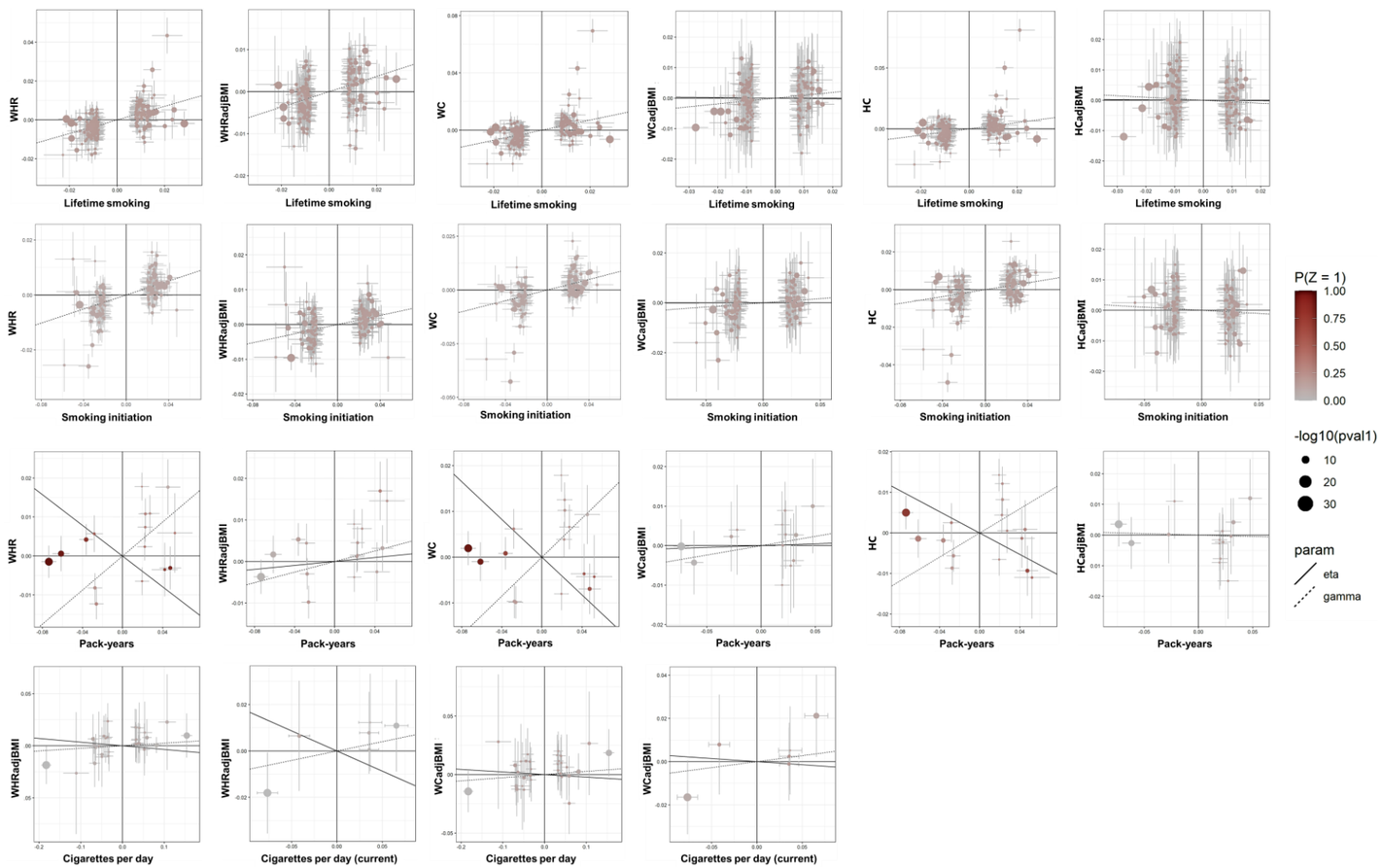
2. Morrison J, Knoblauch N, Marcus JH, Stephens M, He X. Mendelian randomization accounting for correlated and uncorrelated pleiotropic effects using genome-wide summary statistics. Nat Genet. 2020;52(7):740-7. Epub 2020/05/27. doi: 10.1038/s41588-020-0631-4. PubMed PMID: 32451458; PubMed Central PMCID: PMCPMC7343608.
3. Darrous L, Ninon M, and Zoltán K. Simultaneous estimation of bi-directional causal effects and heritable confounding from GWAS summary statistics. Nature communications 12.1 (2021): 1-15.
4. James R Staley, et al. PhenoScanner: a database of human genotype-phenotype associations. Bioinformatics 2016; 32(20):3207-3209
5. Mihir A Kamat, et al. PhenoScanner V2: an expanded tool for searching human genotype-phenotype associations. Bioinformatics 2019; 35(22):4851-4853
6. Sanderson E, Davey Smith G, Windmeijer F, Bowden J. An examination of multivariable Mendelian randomization in the single-sample and two-sample summary data settings. Int J Epidemiol. 2019;48(3):713-27. Epub 2018/12/12. doi: 10.1093/ije/dyy262. PubMed PMID: 30535378; PubMed Central PMCID: PMCPMC6734942.
7. Sanderson E, Spiller W, Bowden J. Testing and correcting for weak and pleiotropic instruments in two-sample multivariable mendelian randomisation. Biorxiv. 2020



8.
9.
10. **Supplementary Figure 1.** Scatter plots showing the effect estimates for smoking traits (x-axis) plotted against the estimates for body fat distribution traits (y-axis) for the causal model using the CAUSE method. The size of the circles indicates the P value of the association of the variant with the smoking trait and the color indicates the P value for the association with the body fat distribution trait. Only variants with $P<5x10^{-8}$ for association with the smoking trait are included in the plot.
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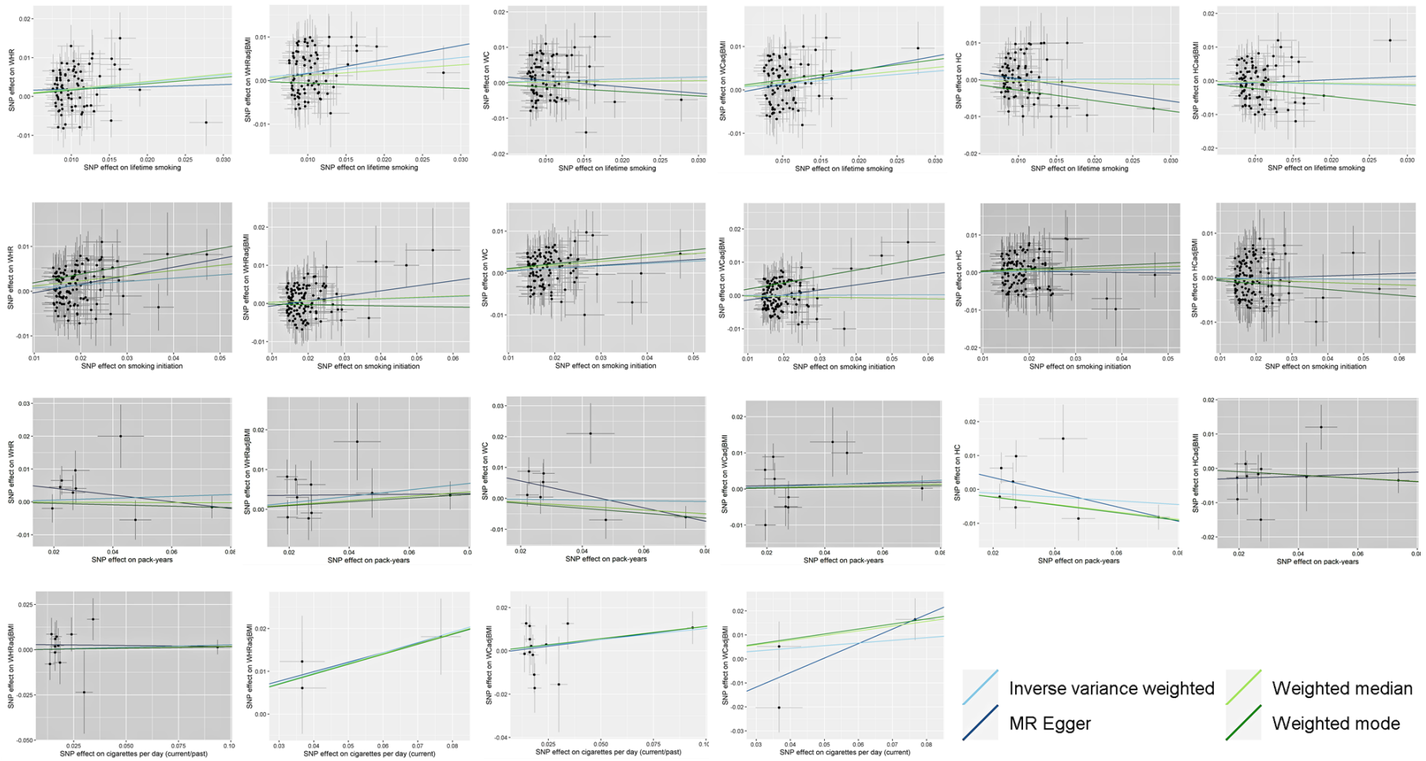
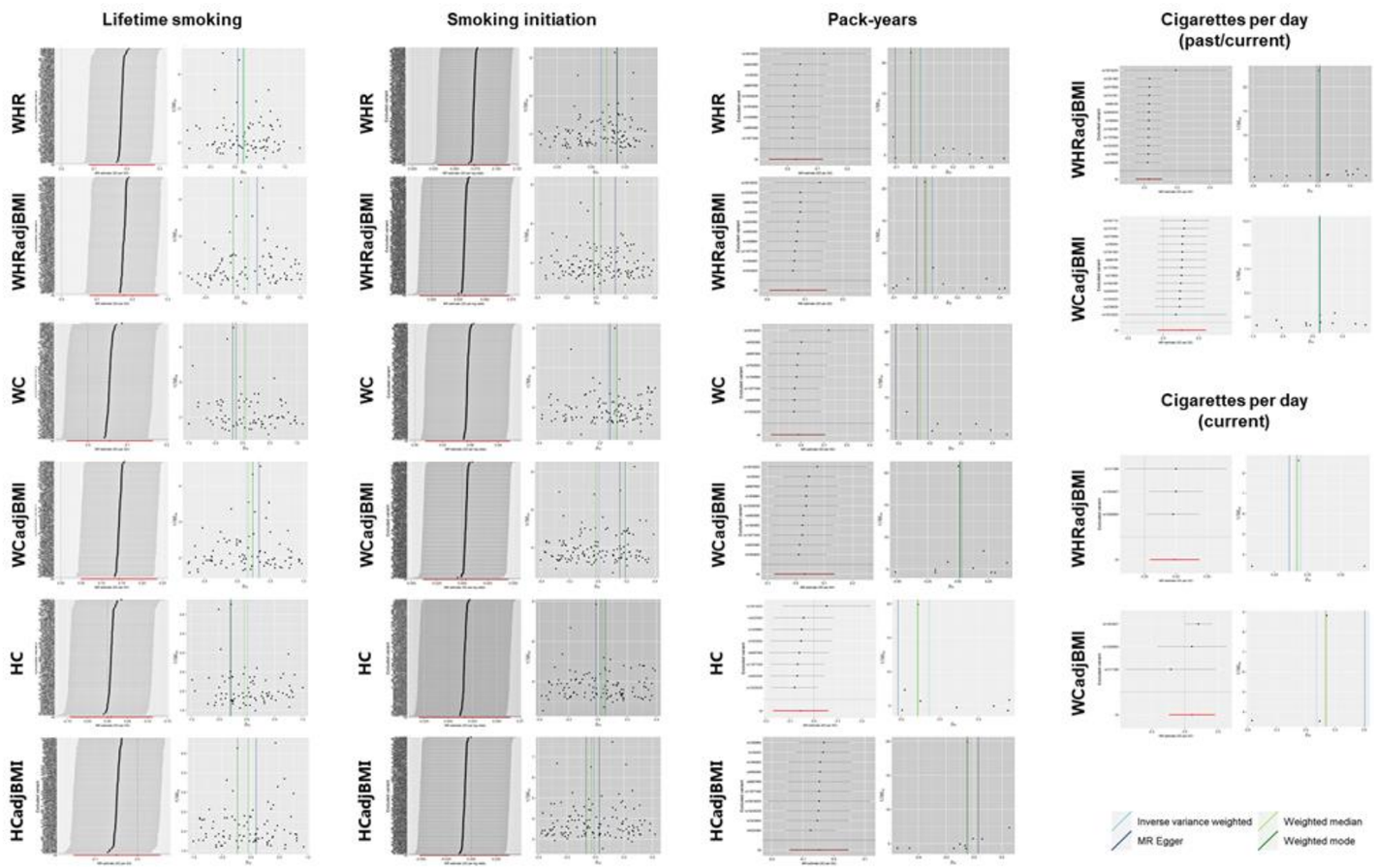
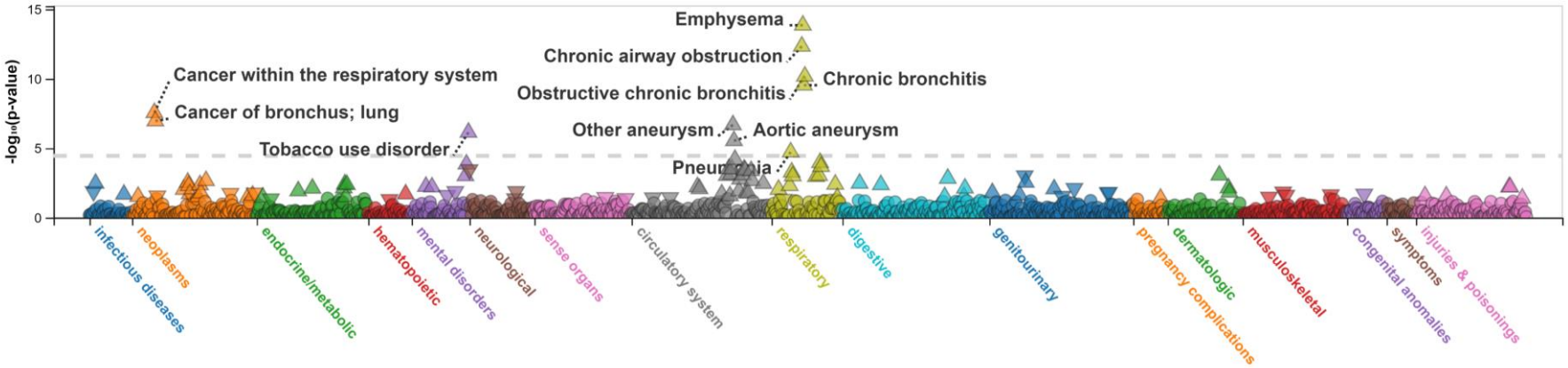


14.

15. **Supplementary Figure 2.** Scatter plots showing the effect estimates for smoking traits (x-axis) plotted against the estimates for body fat distribution traits (y-axis) in the IVW, MR-Egger, weighted median and weighted mode methods after outlier removal and accounting for pleiotropy.



Supplementary Figure 3. Leave-one-out and funnel sensitivity plots for the inverse variance-weighted, MR-Egger, weighted median and weighted mode methods.



Supplementary Figure 4. Phenome-wide association analysis for the rs1317286 (*CHRNA3/5*) variant in the UK Biobank including over 400,000 European-ancestry individuals. Source: http://pheweb.sph.umich.edu/

Supplementary Table 1. Results for Mendelian randomization analyses using the CAUSE method

	Lifetime smoking	Smoking initiation	Pack-years	Lifetime smoking	Smoking initiation	Pack-years	Cigarettes per day (past/current)	Cigarettes per day (current)
-		**WHR**				**WHRadjBMI**		
Median causal effect (95% CI)	0.35 (0.29, 0.41)	0.13 (0.1, 0.16)	0.22 (-0.01, 0.3)	0.18 (0.13, 0.24)	0.07 (0.03, 0.10)	0.06 (0.01, 0.15)	0.02 (-0.1, 0.1)	0.08 (-0.47, 0.27)
Median shared effect (95% CI)	0 (-0.29, 0.27)	0 (-0.15, 0.16)	-0.2 (-0.28, 0.27)	0 (-0.27, 0.24)	0 (-0.16, 0.16)	0.02 (-0.2, 0.31)	-0.04 (-0.7, 0.36)	-0.17 (-1.56, 0.91)
Median q (95% CI)	0.18 (0, 0.86)	0.18 (0, 0.86)	0.3 (0.09, 0.83)	0.18 (0, 0.86)	0.18 (0, 0.86)	0.19 (0, 0.85)	0.14 (0, 0.86)	0.19 (0.01, 0.85)
Sharing vs causal *P*	1.30E-06	2.10E-15	0.85	2.20E-09	5.20E-03	0.13	0.68	0.58
		WC				**WCadjBMI**		
Median causal effect (95% CI)	0.35 (0.29, 0.41)	0.12 (0.09, 0.16)	0.21 (-0.02, 0.28)	0.09 (-0.05, 0.23)	0.03 (-0.04, 0.11)	0.05 (-0.03, 0.15)	0.03 (-0.11, 0.11)	0.06 (-0.27, 0.29)
Median shared effect (95% CI)	0 (-0.29, 0.28)	0 (-0.16, 0.17)	-0.2 (-0.29, 0.27)	-0.01 (-0.63, 0.5)	0 (-0.31, 0.34)	0.01 (-0.43, 0.46)	-0.02 (-0.48, 0.4)	-0.03 (-0.89, 0.74)
Median q (95% CI)	0.18 (0, 0.86)	0.18 (0, 0.86)	0.23 (0.06, 0.86)	0.19 (0, 0.86)	0.19 (0, 0.84)	0.17 (0, 0.86)	0.19 (0, 0.86)	0.22 (0.01, 0.85)
Sharing vs causal *P*	7.70E-12	7.30E-08	0.86	0.15	0.26	0.25	0.71	0.91
		HC				**HCadjBMI**		
Median causal effect (95% CI)	0.26 (0.18, 0.33)	0.09 (0.05, 0.13)	0.15 (-0.03, 0.25)	-0.05 (-0.23, 0.13)	-0.02 (-0.1, 0.05)	-0.01 (-0.13, 0.11)	NA	NA
Median shared effect (95% CI)	0 (-0.31, 0.31)	0 (-0.18, 0.19)	-0.13 (-0.29, 0.26)	-0.01 (-0.72, 0.63)	0 (-0.39, 0.36)	0 (-0.57, 0.6)	NA	NA
Median q (95% CI)	0.19 (0, 0.86)	0.18 (0, 0.86)	0.25 (0.02, 0.86)	0.2 (0.01, 0.86)	0.18 (0, 0.84)	0.17 (0, 0.87)	NA	NA
Sharing vs causal *P*	5.40E-09	1.20E-03	0.79	0.50	0.61	0.99	NA	NA

The results display the results according to the goodness-of-fit for the causal or the sharing model. The median q value indicates the proportion of variants that showed evidence of correlated pleiotropy. WHR, waist-to-hip ratio; WHRAdjBMI, waist-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; CI, confidence interval; NA, not available.

Supplementary Table 2: CAUSE expected log pointwise posterior density (ELPD) results

Smoking trait	Model 1	Model 2	WHR			WHRadjBMI			WC			WCadjBMI			HC			HCadjBMI		
			Delta_ELPD	SE_delta_ELPD	z	Delta_ELPD	SE_delta_ELPD	z	Delta_ELPD	SE_delta_ELPD	z	Delta_ELPD	SE_delta_ELPD	z	Delta_ELPD	SE_delta_ELPD	z	Delta_ELPD	SE_delta_ELPD	z
Lifetime smoking	Null	Sharing	-194.83	15.60	-12.49	-85.62	11.07	-7.73	-184.21	15.22	-12.10	-6.49	3.40	-1.91	-78.45	10.01	-7.84	-0.71	1.53	-0.47
	Null	Causal	-196.28	15.80	-12.42	-86.88	11.27	-7.71	-185.65	15.42	-12.04	-7.08	3.94	-1.80	-79.78	10.23	-7.80	-0.71	2.06	-0.35
	Sharing	Causal	-1.46	0.31	-4.71	-1.26	0.21	-5.87	-1.44	0.21	-6.74	-0.59	0.56	-1.05	-1.34	0.23	-5.72	5.06E-04	0.54	9.32E-04
Smoking initiation	Null	Sharing	-111.83	11.91	-9.39	-53.84	9.58	-5.62	-91.71	10.96	-8.37	-3.52	2.71	-1.30	-39.33	7.19	-5.47	-0.34	1.25	-0.28
	Null	Causal	-113.20	12.07	-9.38	-54.83	9.87	-5.55	-92.94	11.18	-8.31	-3.86	3.20	-1.21	-40.68	7.63	-5.33	-0.20	1.77	-0.11
	Sharing	Causal	-1.37	0.17	-7.85	-0.98	0.38	-2.56	-1.23	0.23	-5.26	-0.35	0.53	-0.65	-1.35	0.44	-3.03	0.15	0.53	0.28
Pack-years	Null	Sharing	-35.29	8.11	-4.35	-8.81	3.76	-2.34	-44.65	8.42	-5.30	-0.76	1.25	-0.60	-20.41	5.63	-3.62	0.67	0.22	3.10
	Null	Causal	-34.47	8.43	-4.09	-9.90	4.44	-2.23	-42.74	9.25	-4.62	-1.36	2.10	-0.65	-18.95	6.57	-2.88	1.53	0.54	2.81
	Sharing	Causal	0.82	0.80	1.03	-1.09	0.98	-1.11	1.91	1.61	1.18	-0.60	0.88	-0.69	1.46	1.81	0.81	0.86	0.35	2.45
Cigarettes per day (past/current)	Null	Sharing	NA	NA	NA	0.47	0.41	1.14	NA	NA	NA	0.42	0.33	1.28	NA	NA	NA	NA	NA	NA
	Null	Causal	NA	NA	NA	0.79	1.09	0.73	NA	NA	NA	0.76	0.94	0.81	NA	NA	NA	NA	NA	NA
	Sharing	Causal	NA	NA	NA	0.32	0.69	0.47	NA	NA	NA	0.34	0.61	0.55	NA	NA	NA	NA	NA	NA
Cigarettes per day (current)	Null	Sharing	NA	NA	NA	0.50	0.38	1.34	NA	NA	NA	0.44	0.12	3.74	NA	NA	NA	NA	NA	NA
	Null	Causal	NA	NA	NA	0.70	1.28	0.55	NA	NA	NA	1.01	0.54	1.87	NA	NA	NA	NA	NA	NA
	Sharing	Causal	NA	NA	NA	0.19	0.92	0.21	NA	NA	NA	0.57	0.43	1.32	NA	NA	NA	NA	NA	NA

WHR, waist-hip ratio; WHRAdjBMI, waist-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; SE, standard error; NA, not available.

Supplementary Table 3: LHC-MR causal effects of heritable shared confounders on smoking and body composition traits

	Confounder term for smoking			Confounder term for adiposity		
Exposure-outcome pairs	**Coefficient**	**SE**	**P-value**	**Coefficient**	**SE**	**P-value**
Lifetime smoking-WHR	0.09	0.01	2.91E-13	-0.08	0.02	2.42E-06
Lifetime smoking-WHRadjBMI	0.07	0.02	1.44E-04	-0.07	0.02	2.01E-05
Lifetime smoking-WC	0.10	0.02	7.03E-06	-0.12	0.03	2.19E-05
Lifetime smoking - WCadjBMI	0.15	0.01	5.86E-27	-0.003	0.01	7.77E-01
Lifetime smoking-HC	0.10	0.02	6.40E-11	-0.11	0.02	3.24E-06
Lifetime smoking - HCadjBMI	0.13	0.01	1.74E-28	0.06	0.03	6.13E-02
Smoking initiation-WHR	0.06	0.01	8.84E-07	-0.06	0.02	6.03E-04
Smoking initiation-WHRadjBMI	0.05	0.01	7.43E-04	-0.06	0.02	7.04E-05
Smoking initiation-WC	0.08	0.01	1.46E-08	-0.12	0.02	1.63E-06
Smoking initiation-WCadjBMI	0.13	0.01	8.06E-36	-0.01	0.01	1.97E-01
Smoking initiation-HC	0.05	0.03	8.35E-02	-0.09	0.04	1.23E-02
Smoking initiation-HCadjBMI	0.10	0.01	3.95E-20	0.05	0.02	2.37E-02
Pack-years-WHR	0.12	0.03	5.82E-05	-0.12	0.02	7.62E-08
Pack-years-WHRadjBMI	0.10	0.03	4.24E-03	-0.09	0.02	8.05E-08
Pack-years-WC	0.11	0.05	0.01	-0.12	0.04	6.82E-04
Pack-years - WCadjBMI	0.22	0.02	7.98E-22	0.004	0.01	7.02E-01
Pack-years-HC	0.12	0.05	0.01	-0.12	0.04	5.12E-03
Pack-years - HCadjBMI	0.15	0.03	1.20E-05	0.03	0.05	4.91E-01
Cigarettes per day (past/current) -WHRadjBMI	0.00	0.03	0.93	-0.18	0.04	1.05E-05
Cigarettes per day (past/current) -WCadjBMI	0.04	0.05	0.42	-0.05	0.08	5.58E-01
Cigarettes per day (current) -WHRadjBMI	0.01	0.12	0.93	0.00	0.13	9.92E-01
Cigarettes per day (current) -WCadjBMI	0.01	0.03	0.72	0.34	0.02	4.35E-55

LHC-MR, Latent Heritable Confounder Mendelian randomization; WHR, waist-hip ratio; WHRAdjBMI, waist-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; SE, standard error.

Supplementary Table 4: LHC-MR bidirectional causal effects between smoking and adiposity traits

	Smoking causal effect on adiposity			Adiposity causal effect on smoking		
Exposure-outcome pairs	**Coefficient**	**SE**	**P-value**	**Coefficient**	**SE**	**P-value**
Lifetime smoking-WHR	0.44	0.03	5.84E-40	0.08	0.02	5.56E-04
Lifetime smoking-WHRadjBMI	0.26	0.03	1.65E-19	-0.01	0.02	0.75
Lifetime smoking-WC	0.42	0.11	1.12E-04	0.14	0.06	0.01
Lifetime smoking-WCadjBMI	0.02	0.02	0.47	0.07	0.04	0.11
Lifetime smoking-HC	0.34	0.07	2.99E-07	0.10	0.03	4.60E-04
Lifetime smoking-HCadjBMI	-0.17	0.03	3.23E-07	-0.03	0.02	0.14
Smoking initiation-WHR	0.49	0.04	5.58E-33	0.01	0.02	0.63
Smoking initiation-WHRadjBMI	0.31	0.03	1.70E-29	-0.02	0.01	0.13
Smoking initiation-WC	0.37	0.12	1.77E-03	0.12	0.04	3.33E-03
Smoking initiation-WCadjBMI	0.07	0.02	5.32E-04	0.03	0.03	0.38
Smoking initiation-HC	0.15	0.22	5.02E-01	0.11	0.04	9.21E-03
Smoking initiation-HC	-0.08	0.03	9.05E-03	4.67E-03	0.02	0.76
Pack-years-WHR	0.37	0.10	3.26E-04	0.27	0.03	3.58E-18
Pack-years-WHRadjBMI	0.24	0.05	7.90E-06	0.07	0.02	2.53E-03
Pack-years-WC	0.25	0.20	0.22	0.32	0.04	5.14E-16
Pack-years-WCadjBMI	-0.01	0.02	7.41E-01	0.16	0.05	4.50E-03
Pack-years-HC	0.43	0.20	0.04	0.17	0.05	1.85E-03
Pack-years-HCadjBMI	-0.13	0.06	0.04	-0.02	0.07	0.81
Cigarettes per day (past/current)-WHRadjBMI	0.06	0.10	0.55	0.24	0.07	2.75E-04
Cigarettes per day (past/current)-WCadjBMI	-0.11	0.16	0.48	0.15	0.07	0.04
Cigarettes per day (current)-WHRadjBMI	0.24	0.16	0.13	0.25	0.28	0.37
Cigarettes per day (current)-WCadjBMI	-0.36	0.19	0.06	0.33	0.11	3.34E-03

LHC-MR, Latent Heritable Confounder Mendelian randomization; WHR, waist-hip ratio; WHRAdjBMI, waist-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; SE, standard error.

Supplementary table 5. Mendelian randomization results using the IVW, Egger, weighted median and weighted mode methods

		WHR				WHRAdjBMI				WC				WCAdjBMI				HC				HCadjBMI			
Exposure	**Model**	**SNP**	**Beta**	**SE**	**p-value**	**SNP**	**beta**	**SE**	**p-value**	**SNP**	**beta**	**SE**	**p-value**	**SNP**	**beta**	**SE**	**p-value**	**SNP**	**beta**	**SE**	**p-value**	**SNP**	**beta**	**SE**	**p-value**
Lifetime smoking	IVW	83	0.18	0.05	2.28E-04	83	0.18	0.05	0.0004	80	0.06	0.06	0.33	86	0.14	0.05	2.74E-03	81	0.01	0.05	0.87	89	-0.05	0.05	0.36
	Egger	83	0.06	0.21	0.78	83	0.32	0.20	0.12	80	-0.18	0.22	0.40	86	0.33	0.19	0.09	81	-0.30	0.21	0.16	89	0.09	0.21	0.66
	Weighted median	83	0.20	0.08	1.00E-02	83	0.12	0.08	0.11	80	0.02	0.08	0.80	86	0.17	0.07	0.02	81	-0.04	0.08	0.59	89	-0.04	0.08	0.65
	Weighted mode	83	0.17	0.21	0.44	83	-0.06	0.16	0.72	80	-0.12	0.17	0.47	86	0.23	0.13	0.08	81	-0.28	0.18	0.12	89	-0.23	0.27	0.39
Smoking initiation	IVW	121	0.07	0.02	8.96E-04	130	0.03	0.02	0.15	115	0.06	0.02	0.01	131	3.51E-03	0.02	0.87	116	0.02	0.02	0.48	127	-0.01	0.02	0.77
	Egger	121	0.19	0.10	0.06	130	0.13	0.09	0.16	115	0.07	0.10	0.52	131	0.15	0.09	0.10	116	-0.01	0.11	0.90	127	0.03	0.10	0.78
	Weighted median	121	0.12	0.03	1.15E-04	130	0.03	0.03	0.29	115	0.09	0.03	0.01	131	-0.02	0.03	0.61	116	0.03	0.03	0.35	127	-0.03	0.03	0.41
	Weighted mode	121	0.19	0.09	0.03	130	-0.02	0.08	0.85	115	0.11	0.09	0.21	131	0.19	0.10	0.05	116	0.05	0.09	0.57	127	-0.07	0.10	0.50
Pack years of adult smoking	IVW	9	0.03	0.05	0.55	10	0.08	0.04	0.04	8	-0.22	0.10	0.07	10	0.03	0.05	0.58	8	-0.06	0.06	0.34	10	-0.05	0.05	0.33
	Egger	9	-0.10	0.08	0.26	10	0.01	0.08	0.93	8	-0.22	0.10	0.07	10	0.02	0.11	0.89	8	-0.21	0.11	0.10	10	0.03	0.10	0.76
	Weighted median	9	-2.44E-03	0.04	0.95	10	0.05	0.04	0.20	8	-0.06	0.04	0.16	10	0.02	0.05	0.71	8	-0.11	0.05	0.03	10	-0.05	0.05	0.32
	Weighted mode	9	-0.02	0.04	0.62	10	0.05	0.05	0.34	8	-0.08	0.05	0.13	10	0.01	0.05	0.81	8	-0.11	0.05	0.05	10	-0.05	0.05	0.34
Cigarettes per day (past/current)	IVW	NA	NA	NA	NA	12	0.03	0.04	0.50	NA	NA	NA	NA	13	0.10	0.07	0.14	NA	NA	NA	NA	NA	NA	NA	NA
	Egger	NA	NA	NA	NA	12	-0.01	0.07	0.87	NA	NA	NA	NA	13	0.12	0.10	0.26	NA	NA	NA	NA	NA	NA	NA	NA
	Weighted median	NA	NA	NA	NA	12	0.02	0.04	0.64	NA	NA	NA	NA	13	0.11	0.08	0.15	NA	NA	NA	NA	NA	NA	NA	NA
	Weighted mode	NA	NA	NA	NA	12	0.02	0.05	0.72	NA	NA	NA	NA	13	0.11	0.08	0.17	NA	NA	NA	NA	NA	NA	NA	NA
Cigarettes per day (current)	IVW	NA	NA	NA	NA	3	0.24	0.10	0.02	NA	NA	NA	NA	3	0.11	0.18	0.53	NA	NA	NA	NA	NA	NA	NA	NA
	Egger	NA	NA	NA	NA	3	0.22	0.29	0.59	NA	NA	NA	NA	3	0.60	0.50	0.44	NA	NA	NA	NA	NA	NA	NA	NA
	Weighted median	NA	NA	NA	NA	3	0.24	0.10	0.02	NA	NA	NA	NA	3	0.20	0.11	0.07	NA	NA	NA	NA	NA	NA	NA	NA
	Weighted mode	NA	NA	NA	NA	3	0.23	0.12	0.18	NA	NA	NA	NA	3	0.21	0.11	0.20	NA	NA	NA	NA	NA	NA	NA	NA

WHR, waist-hip ratio; WHRAdjBMI, waist-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; SE, standard error; NA, not available.

Supplementary Table 6. Sensitivity tests for IVW, Egger, weighted median and weighted mode Mendelian randomization methods

		WHR		WHRAdjBMI		WC		WCAdjBMI		HC		HCadjBMI	
Smoking trait	**Sensitivity test**	**Estimate**	**p-value/CI**	**Estimate**	**p-value/CI**	**Estimate**	**p-value/CI**	**Estimate**	**p-value/CI**	**Estimate**	**p-value/CI**	**Estimate**	**p-value/CI**
Lifetime smoking	Q (p-value)	87.29	0.32	80.69	0.49	90.85	0.17	73.48	0.81	73.23	0.66	94.68	0.27
	I2 (CI)	6.10	0%; 28,60%	0	0%; 26,40%	13.00	0%; 34,80%	0	0%; 14,50%	0	0%; 21,20%	8,10%	0%; 30,10%
	Q-Q' (p-value)	0.47	0.50	0.57	0.45	1.57	0.21	0.97	0.32	2.29	0.13	0.57	0.47
	Egger intercept	1,36-03	0.50	-1.56E-03	0.45	2.52E-03	0.21	-1.98E-03	0.30	3.29E-03	0.12	-1.51E-03	0.47
	Rucker test	IVW		IVW		IVW		IVW		IVW		IVW	
Smoking initiation	Q (p-value)	70.77	1.00	70.11	1	65.16	1.00	87.20	1.00	68.44	1.00	80.59	0.9994
	I2 (CI)	0	0%; 0%	0	0%; 0%	0	0%; 0%	0	0%; 0%	0	0%; 0%	0	0%; 0%
	Q-Q' (p-value)	1.45	0.23	1.26	0.26	0.01	0.91	2.76	0.10	0.08	0.78	0.13	0.72
	Egger intercept	-2.22E-03	0.12	-1.94E-03	0.13	-2.18E-04	0.88	-2.85E-03	0.04	5.68E-04	0.72	-6.55E-04	0.66
	Rucker test	IVW		IVW		IVW		IVW		IVW		IVW	
Pack-years	Q (p-value)	11.56	0.1717	8.82	0.4540	15.20	0.03	16.91	0.05	13.69	0.06	12.15%	0.2047
	I2 (CI)	30.80	0%; 68,00%	0	0%; 62.40%	53.90	0; 79,20%	46.80%	0%; 74,40%	48,80%	0%; 77,20%	26.00%	0,00%; 64,30%
	Q-Q' (p-value)	3.94	4.72E-02	1.33	0.25	0.01	5.35E-03	0.05	0.83	4.41	0.04	-3.51E-03	0.25
	Egger intercept	6.25E-03	4.72E-02	3.37E-03	0.25	7.76	5.35E-03	6.35E-04	0.83	7.81E-03	0.04	1.31	0.25
	Rucker test	IVW		IVW		IVW		IVW		IVW		IVW	
Cigarettes per day (past/current)	Q (p-value)	NA	NA	6.82	0.81	NA	NA	9.35	0.67	NA	NA	NA	NA
	I2 (CI)	NA	NA	0	0,00%; 32,80%	NA	NA	0%	0,00%; 44,30%	NA	NA	NA	NA
	Q-Q' (p-value)	NA	NA	0.58	0.45	NA	NA	0.06	0.81	NA	NA	NA	NA
	Egger intercept	NA	NA	2.95E-03	0.34	NA	NA	-9.32E-04	0.80	NA	NA	NA	NA
	Rucker test	NA		IVW		NA		IVW		NA		NA	
Cigarettes per day (current)	Q (p-value)	NA	NA	0.17	0.92	NA	NA	5.76	0.06	NA	NA	NA	NA
	I2 (CI)	NA	NA	0	0%; 0%	NA	NA	65,30%	0,00%; 90,00%	NA	NA	NA	NA
	Q-Q' (p-value)	NA	NA	3.91E-03	0.95	NA	NA	3.42	0.06	NA	NA	NA	NA
	Egger intercept	NA	NA	1.04E-03	0.88	NA	NA	-0.03	0.06	NA	NA	NA	NA
	Rucker test	NA		IVW		NA		IVW		NA		NA	

WHR, waist-hip ratio; WHRAdjBMI, waist- hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; NA, not available.

Supplementary Table 7: Multivariable Mendelian randomization results between lifetime smoking and education with abdominal adiposity traits

Trait	SNP	mF	Cochran's Q (P-value)	beta	SE	P-value
WHR						
Lifetime Smoking	207	11.04	163.70	0.36	0.06	9,43E-10
Education	207	18.87	0.98	-0.28	0.05	2,09E-07
WHRadjBMI						
Lifetime Smoking	212	12.02	190.54	0.29	0.06	6,27E-07
Education	212	19.64	0.82	-0.12	0.06	0.03
WC						
Lifetime Smoking	199	10.27	184.07	0.38	0.07	2.68E-08
Education	199	17.54	0.72	-0.27	0.06	1.19E-05
WCadjBMI						
Lifetime Smoking	204	12.55	169.82	0.22	0.05	5.91E-05
Education	204	20.89	0.95	0.09	0.05	0.11
HC						
Lifetime Smoking	195	10.16	181.14	0.19	0.07	6.36E-03
Education	195	17.58	0.70	-0.15	0.06	0.02
HCadjBMI						
Lifetime Smoking	199	12.80	183.57	-0.05	0.06	0.36
Education	199	21.77	0.73	0.20	0.06	8.60E-04

WHR, waist-to-hip ratio; WHRAdjBMI, waist-to-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index.

Supplementary Table 8: Multivariable Mendelian randomization results between smoking initiation and education with abdominal adiposity traits

Trait	SNP	mF	Cochran's Q (P-value)	beta	SE	P-value
WHR						
Smoking initiation	207	10.57	167.30	0.10	0.02	1.28E-05
Education	207	28.25	0.97	-0.38	0.05	9.74E-14
WHRadjBMI						
Smoking initiation	207	11.33	164.67	0.09	0.02	1.30E-04
Education	207	27.34	0.98	-0.15	0.05	2.70E-03
WC						
Smoking initiation	195	10.19	179.54	0.08	0.03	2.31E-03
Education	195	26.39	0.73	-0.36	0.05	3.29E-10
WCadjBMI						
Smoking initiation	202	10.84	167.31	0.06	0.02	7.59E-03
Education	202	26.64	0.95	0.05	0.05	2.71E-01
HC						
Smoking initiation	194	10.56	189.92	0.05	0.03	7.41E-02
Education	194	27.84	0.51	-0.27	0.06	5.84E-06
HCadjBMI						
Smoking initiation	196	11.27	164.15	-0.01	0.02	0.63
Education	196	27.71	0.94	0.19	0.05	3.57E-04

WHR, waist-to-hip ratio; WHRAdjBMI, waist-to-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index.

Supplementary Table 9: Wald ratio estimates for the association between smoking and body fat distribution traits for the rs1317286 variant in the *CHRNA5/3* locus

		WHR			WHRadjBMI			WC			WCadjBMI			HC			HCadjBMI		
Smoking trait	**F-statistic**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**	**beta**	**SE**	**p-value**
Lifetime smoking	157.94	0.13	0.24	0.59	0.49	0.24	0.04	-0.29	0.24	0.24	0.32	0.24	0.17	-0.50	0.25	0.05	-0.16	0.25	0.51
Smoking initiation	6.78	-0.24	0.45	0.59	-0.92	0.45	0.04	0.54	0.46	0.24	-0.61	0.45	0.17	0.94	0.47	0.05	0.31	0.47	0.51
Pack years adult smoking	401.53	0.03	0.06	0.59	0.12	0.06	0.04	-0.07	0.06	0.24	0.08	0.06	0.17	-0.13	0.06	0.05	-0.04	0.06	0.51
Cigarettes per day (past/current)	925.99	NA	NA	NA	0.10	0.05	0.04	NA	NA	NA	0.09	0.05	0.06	NA	NA	NA	NA	NA	NA
Cigarettes per day (current)	178.58	NA	NA	NA	0.24	0.12	0.04	NA	NA	NA	0.22	0.11	0.06	NA	NA	NA	NA	NA	NA

WHR, waist-to-hip ratio; WHRAdjBMI, waist-to-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index; SE, standard error; NA, not available.

Supplementary Table 10: Datasets for smoking and body fat distribution traits used in the present study

Trait and MR Method	Author	Sample size	Population/note
Lifetime smoking			
CAUSE, LHC-MR, 2SMR and MVMR	Wootton et al 2020	462,690	European individuals from UK Biobank
Smoking Initiation			
CAUSE, LHC-MR, and MVMR	Liu et al 2019	632,802	European individuals from GSGC-UKBB meta-analysis without 23andMe.
2SMR	Liu et al 2019	1,232,091	European individuals from GSGC-UKBB meta-analysis with 23andMe.
Pack-years			
CAUSE and LHC-MR	Elseworth et al 2018	142,387	European individuals from UK Biobank
2SMR	Elseworth et al 2019	142,387	European individuals from UK Biobank
Cigarettes per day (past and current)			
CAUSE and LHC-MR	Liu et al 2019	263,954	European individuals from GSGC-UKBB meta-analysis without 23andMe.
2SMR	Liu et al 2019	337,334	European individuals from GSGC-UKBB meta-analysis with 23andMe.
Cigarettes per day (current)			
CAUSE and LHC-MR	Elseworth et al 2018	33,229	European individuals from UK Biobank
2SMR	Elseworth et al 2018	33,229	European individuals from UK Biobank
WHR			
CAUSE and LHC-MR	Pulit et al 2019	697,734	European individuals from GIANT-UK Biobank meta-analysis
2SMR and MVMR	Shungin et al 2015	212,248	European individuals from GIANT
WHRadjBMI			
CAUSE and LHC-MR	Pulit et al 2019	694,649	European individuals from GIANT-UK Biobank meta-analysis
2SMR and MVMR	Shungin et al 2015	210,086	European individuals from GIANT. Used for lifetime smoking and smoking initiation.
WC			
CAUSE and LHC-MR	Elseworth et al 2018	462,166	European individuals from UKBB
2SMR and MVMR	Shungin et al 2015	232,101	European individuals from GIANT
WCadjBMI			
CAUSE, LHC-MR, 2SMR and MVMR	Shungin et al 2015	231,355	European individuals from UKBB
WHRadjBMI stratified for smokers			

CAUSE and LHC-MR	Justice et al 2017	40,543	European individuals. Used for cigarettes per day analysis
2SMR	Justice et al 2017	40,543	European individuals. Used for cigarettes per day analysis
WCadjBMI stratified for smokers			
CAUSE and LHC-MR	Justice et al 2017	43,226	European individuals. Used for cigarettes per day analysis
2SMR	Justice et al 2017	43,226	European individuals. Used for cigarettes per day analysis
HC			
CAUSE and LHC-MR	Elseworth et al 2018	462,117	European individuals from UKBB
2SMR and MVMR	Shungin et al 2015	213,038	European individuals from GIANT
HCadjBMI			
CAUSE and LHC-MR	Shungin et al 2015	211,117	European individuals from GIANT
2SMR and MVMR	Shungin et al 2015	211,117	European individuals from GIANT. Used for lifetime smoking and smoking initiation.

CAUSE, Causal Analysis Using Summary Effect Estimates; 2SMR, two-sample Mendelian randomization; MVMR, multivariable Mendelian randomization; LHC-MR, Latent Heritable Confounder Mendelian randomization; WHR, waist-hip ratio; WHRAdjBMI, waist-hip ratio adjusted for body mass index; WC, waist circumference; WCadjBMI, waist circumference adjusted for body mass index; HC, hip circumference; HCadjBMI, hip circumference adjusted for body mass index.