

# Evaluation of the causality between testosterone, obesity, and diabetes

Euichan Shin<sup>1</sup>, Ali Alamdar Shah Syed<sup>2</sup>

<sup>1</sup> The Semiconductor-Manufacturing International Corporation (SMIC) Private School, Shanghai, China

<sup>2</sup> Shanghai Jiaotong University, Shanghai, China

## SUMMARY

While the effect of testosterone on male sex characteristics is well-known, its relationship with non-communicable diseases (NCDs) – particularly obesity and type 2 diabetes (T2D) – is less concrete. Furthermore, testosterone may yield sex-specific results on such NCDs. We employed Mendelian randomization (MR) analysis on publicly available patients' genomic data to evaluate the causality between testosterone, obesity, and T2D within combined, male, and female sex-stratified settings. Our results demonstrated that T2D significantly increased and was increased by heightened levels of obesity. Furthermore, we also found that male testosterone likely reduces obesity and T2D, while female testosterone significantly increases body fat and blood glucose levels. This research presents sex-based discrepancies that could hold significance in future clinical applications of testosterone. This research also highlights the potential in sex-stratifying two-sample MR analyses for future studies.

## INTRODUCTION

Testosterone is the primary sex hormone in males, responsible for the development and growth of primary and secondary male sex characteristics (1). Divided into bioavailable and sex hormone binding globulin (SHBG)-bound testosterone, fluctuations in an individual's total testosterone concentration may not only affect male qualities – such as erectile function and spermatogenesis – but cause ill-health for both sexes (2). For instance, clinical hypogonadism (defined as a morning testosterone concentration below 300 ng/dL in males and 15 ng/dL in females) has been shown to cause depressed moods and poorer concentration; some studies have found a correlation between testosterone deficiency and increases in mortality rates by up to 40% (3,4). Female hypogonadism also results in abnormal sexual characteristics, including lacking breast tissue, loss of menstrual periods, and decreased libido (2). With the international consensus that there is a natural decline in testosterone production in both sexes at a rate of about 1.3% in males and 1% in females per year, hypogonadism and its effects may be inevitable (5,6,7). It is important to note that fluctuations in bioavailable testosterone between the two testosterone types is widely believed to dominantly cause the aforementioned symptoms. The latter is testosterone bound to SHBG molecules that travel the bloodstream, and this bound state inhibits the effects of the hormone (8).

Particularly, a deficiency in testosterone production may

result in an increased risk in type 2 diabetes mellitus (T2D), a chronic condition and the major form of diabetes characterized by high blood sugar, low insulin production, and insulin resistance (9). Whereas healthy individuals have a blood sugar level of below 140 mg/dL, the blood of diabetics is 200 mg/dL or higher, commonly resulting in fatigue, blurred vision, cardiovascular complications, and frequent urination (10). Some studies have found that T2D patients commonly have significantly lower endogenous testosterone concentrations compared to non-diabetics; however, others have found that there is no obvious correlation between fluctuations in testosterone levels and risk of diabetes (11,12). Therefore, the evidence surrounding this relationship remains controversial. Another study has discovered that high testosterone may influence glycemic status positively in males and negatively in females, suggesting that the relationship may be inverse across the two sexes (13).

Obesity, a universally recognized disease characterized by an excessive accumulation of body fat and clinically defined as a Body Mass Index (BMI) reading over 30 kg/m<sup>2</sup>, is a strongly associated risk factor and symptom of T2D (14). Adipose tissue buildup in obese individuals secrete leptin, glycerol, proinflammatory signaling molecules, and non-esterified fatty acids (NEFAs), which all lead to decreased insulin sensitivity in  $\beta$ -cells (15). Conversely, the elevated blood glucose levels induced by  $\beta$ -cell dysfunction are stored as fatty acids to be converted into adipose tissue (14). Testosterone's relationship to obesity is also not obvious. There appears to be conflicting findings on the relationship between increased body fat and testosterone levels, where obese men are characterized by hypogonadism, while obese women often undergo conditions of hypergonadism (morning testosterone concentrations exceeding 70 ng/dL) (16).

Therefore, the existing research suggests that abnormally low testosterone concentrations in males and females may pose opposite effects on risk of T2D and obesity – which have been concretely established to complement one another. On the other hand, it may also hold no significant association with either trait in males or females. Identifying the relationships between testosterone and these NCDs will be beneficial to uncovering the effect of naturally declining testosterone concentration with age, as well as for delivering appropriate hormonal treatments.

One biostatistical technique used in medical research to evaluate the significant relationships between physiological instruments is Mendelian randomization (MR). MR can be used to uncover significant causal relationships between variables without the feasibility concerns of randomized controlled trials (RCTs) through using randomized genetic instruments to minimize the influence of confounding factors (17). By drawing publicly available genetic data from

the genome wide association studies (GWAS) catalog, researchers can analyze relationships between an array of clinical conditions and genetic characteristics (18). With male testosterone in particular, previous studies have explored associations between testosterone and a variety of non-communicable diseases such as gout, bipolar disorder, Alzheimer’s disease, cardiovascular diseases, as well as prostate and breast cancer (19).

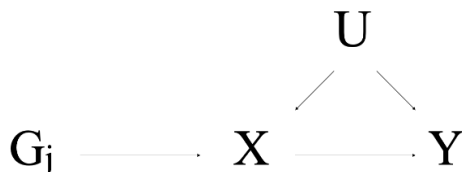
Ultimately aiming to verify the triangular relationship between these three variables, we utilized two-sample MR to explore the sex-specific relationships between bioavailable and total testosterone, obesity – measured by BMI and waist-to-hip ratio (WHR) – and risk of T2D. We hypothesized that the results would align with the general proposition of previous studies, which suggests that male testosterone generally decreases risk of T2D and obesity, whereas female testosterone increases the two diseases. Moreover, obesity and T2D, due to the positive feedback loop between the two diseases, should cause an increase in one another. At the time of publication, our study is the first known effort to implement MR to study the causality between these three variables.

Despite a few insignificant results, our findings generally aligned with the expectations that the influence of testosterone on T2D and obesity would be inverse in males and females. Furthermore, as expected, total testosterone was less definite in its effects than bioavailable (active) testosterone as total testosterone also relates to the concentration of SHBG-bound (inactive) testosterone. These converse results underscore appropriate administration of hormonal treatment based on the patient’s sex.

**RESULTS**

To better understand the effect of changes in testosterone concentration on obesity and T2D in males and females, we employed a bi-directional MR analysis for genetic predictors of testosterone levels. The MR technique is an alternative to randomized controlled trials (RCTs) that can help determine causality between two variables. Due to the costs and ethical concerns behind large-scale RCTs, relying on genetic instruments can be a powerful alternative to exploring how certain traits or behaviors can lead to a specific outcome determined by a birth-assigned allele. In other words, genetic variants associated with the exposure trait can help determine whether the exposure can cause another response trait – in this case, testosterone affecting obesity and T2D – without the effect of confounding factors (Figure 1).

To begin, we took measures to satisfy the three underlying conditions necessary to conduct a MR study.



**Figure 1: Principles of using genetic instruments to determine causality.** Genetic instruments (Gj) represent the exposure (X) which affects the outcome (Y) without the influence of confounders (U). By using Gj to directly influence X, the effect of confounders U can be minimized to arrive at a significant conclusion on the relationship between X and Y.

First, the genetic variant must be strongly associated with the exposure. To satisfy the first condition, we extracted genome-wide significant SNPs from the exposure GWAS. Second, the genetic variant must not be correlated with confounding factors in the exposure-outcome relationship. By using a large, randomized sample of genetic variants, we were able to examine the impact of genetic variants on increase in exposure while randomizing the impact of confounding variables. Finally, the genetic variant must only influence the outcome variable through the exposure; in other words, the instrument must not display pleiotropy (20). The MR-Egger intercept method was used to satisfy this assumption (18). Through this method, if the intercept of exposure-outcome relationship is significantly different from zero, then the result is considered to show pleiotropy and deemed invalid.

We obtained publicly available sex-stratified GWAS data from the GWAS catalog and a search for existing literature. Then, we conducted a total of 48 two-sample MR analyses across 12 sex-specific testosterone and obesity datasets and 1 combined T2D dataset (21,22,23).

We implemented two types of testosterone measurement, total and bioavailable testosterone. We used genetic instruments for waist-to-hip ratio (WHR) and body mass index (BMI) to quantify obesity. A genetic instrument for risk of T2D was created using single nucleotide polymorphisms (SNPs) that were associated with T2D on a genome wide significance level (24). We obtained and evaluated sex-stratified data for the testosterone and obesity variables from the GWAS catalog and previous MR studies utilizing these datasets (21, 22, 23). As for T2D, sex-stratified GWAS data was not publicly available, so the most recent GWAS with combined male and female samples was used.

There were two primary findings in the combined dataset. First, increases in total testosterone (T.T.) and bioavailable testosterone (B.T.) indicated significant correlations to increases in both T2D and obesity. Increased T.T. indicated reductions in WHR ( $p = 0.0104$ ) and, conversely, increased WHR demonstrated reductions in T.T. levels ( $p < 0.001$ ). Increased BMI decreases T.T. ( $p < 0.001$ ), although T.T. had no significant effect on BMI. Increased B.T. has a mutually

Exposure	Response	nSNP	Beta	P-value
B.T.	WHR	124	7.46E-02	3.45E-02
WHR	B.T.	449	5.12E-02	3.89E-07
T2D	B.T.	141	3.38E-02	1.60E-05
T.T.	WHR	227	-1.40E-01	1.04E-02
T.T.	T2D	208	-4.47E-01	9.03E-04
WHR	T.T.	449	-4.98E-02	2.67E-10
T2D	T.T.	141	-2.83E-02	8.19E-06

**Table 1: Significant bioavailable and total testosterone relationships from the combined dataset.** The 7 different significant effects of a modifiable exposure variable on a response. nSNP represents the number of SNPs evaluated within the instruments. The beta represents the directionality of the relationship, with a positive (beta > 0) value indicating an increase in the response variable, whereas a negative (beta < 0) value indicating a decrease. A p-value < 0.05 indicates a significant correlation.

positive relationship with both measures of adipose tissue buildup, increasing WHR ( $p = 0.0345$ ) and BMI ( $p = 3.47E-03$ ), and being increased by increased WHR ( $p < 0.001$ ) and BMI ( $p < 0.001$ ). Rise in T.T. decreases ( $p < 0.001$ ) and is decreased by ( $p < 0.001$ ) T2D, where B.T. is significantly increased by increased T2D ( $p < 0.001$ ). The results also supported the well-established relationship between obesity and diabetes, with increased T2D correlating with an increase in ( $p < 0.001$ ) and was increased by ( $p < 0.001$ ) WHR. Similarly, higher levels of BMI increased risk of T2D ( $p < 0.001$ ), although increased risk of T2D did not yield a significant result on BMI levels (**Table 1**).

In the male dataset, increased T.T. and B.T. both generally decreased obesity and risk of diabetes. Increased BMI decreased T.T. ( $p < 0.001$ ) and B.T. ( $p < 0.001$ ); in the reverse direction, rise in T.T. ( $p < 0.001$ ) and B.T. ( $p = 3.51E-02$ ) caused a decrease in BMI as well. Heightened WHR significantly decreased T.T. ( $p = 3.05E-03$ ). Increased T.T. in males decreased ( $p < 0.001$ ) and was decreased by ( $p < 0.001$ ) the genetic instruments in the combined T2D dataset. Similar to the combined results, increased WHR ( $p = 7.78E-03$ ) and BMI ( $p < 0.001$ ) both increased T2D risk in males, and risk in risk of T2D only significantly increased WHR ( $p = 4.51E-03$ ) (**Table 2**).

In females, rise in B.T. increased both BMI ( $p < 0.001$ ) and WHR ( $p < 0.001$ ). Increased BMI ( $p < 0.001$ ) and WHR ( $p < 0.001$ ) increased B.T. as well. As for T.T., increased BMI increased ( $p < 0.001$ ) and was increased by ( $p = 2.73E-03$ ) female total testosterone; however, increased WHR decreased T.T. ( $p < 0.001$ ). Increased bioavailable testosterone in females increased risk of T2D ( $p < 0.001$ ), and increased T2D also caused an increase in B.T. ( $p < 0.001$ ). In alignment with the previous two relationships between obesity and T2D, increases in WHR positively affected ( $p < 0.001$ ) and was affected by ( $p < 0.001$ ) T2D. Rise in BMI levels increased risk of T2D ( $p < 0.001$ ) (**Table 3**).

In summary, our results support the correlation between increased obesity and T2D. Furthermore, we found that male testosterone generally led to declines in obesity and T2D, and vice versa. However, in females, testosterone seemed to significantly increase and become increased by such NCDs (**Figure 2**).

## DISCUSSION

The results of this study support a positive bidirectional relationship between obesity and T2D for all examined datasets. As expected, increased WHR and BMI were both predictive of and predicted by increased risk of T2D. Moreover, a greater BMI was correlated with a larger risk of developing T2D. As aforementioned, this relationship is bolstered by the biological mechanisms between the two diseases. As adipose tissues secrete proinflammatory signaling molecules and non-esterified fatty acids, excessive body fat can decrease insulin sensitivity in tissues like muscle and liver cells (25). The  $\beta$ -cells of the pancreas may also be impaired, affecting insulin production (14). This could create an excess of blood glucose that builds into adipose tissue, enhancing body fat levels (24).

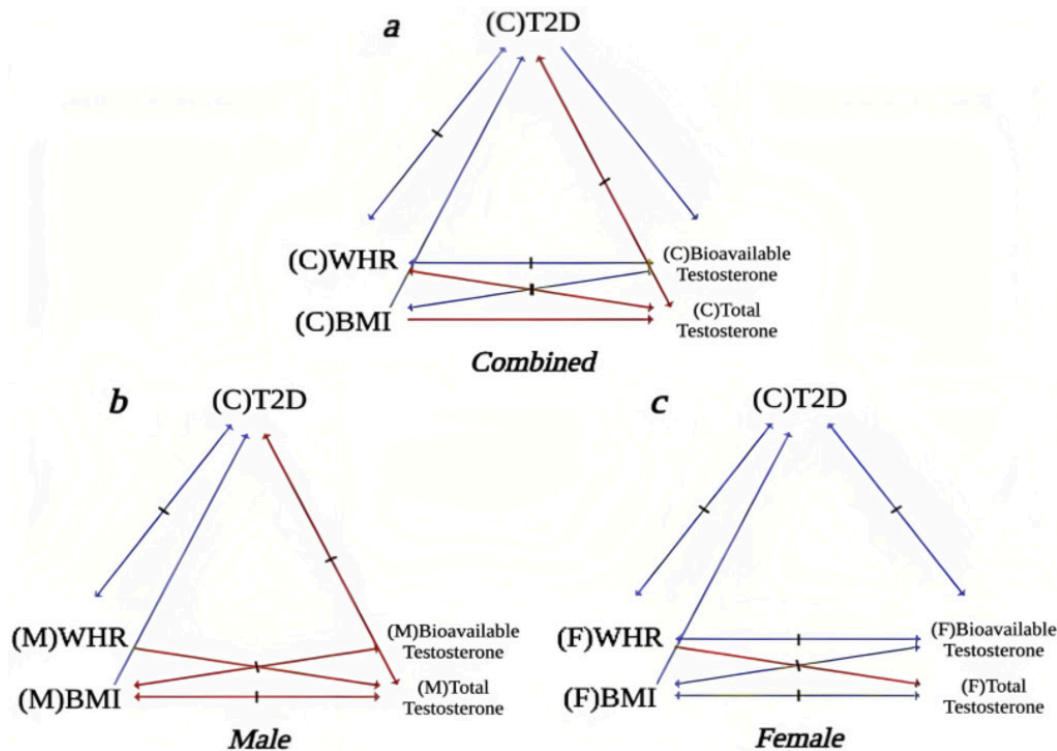
More interestingly, the results demonstrated that changes in testosterone concentration in males and females may affect the aforementioned diseases in opposite manners. In males, increased B.T. decreased both BMI and WHR, and

Exposure	Outcome	nSNP	Beta	P-value
BMI	B.T.	364	-1.21E-01	4.83E-14
BMI	T2D	333	7.81E-01	3.26E-28
WHR	T2D	130	3.19E-01	7.77E-03
B.T.	BMI	122	-5.25E-02	3.5E-02
T2D	WHR	138	3.16E-02	4.51E-03
T.T.	BMI	222	-6.29E-03	3.36E-04
T.T.	T2D	203	-1.85E-01	6.90E-04
BMI	T.T.	364	-2.58E-01	2.21E-35
WHR	T.T.	137	-8.63E-02	3.05E-03
T2D	T.T.	141	-7.88E-02	6.63E-08

**Table 2: Significant bioavailable and total testosterone relationships from the male dataset.** A summary of the 10 significant relationships found in the male dataset. nSNP represents the number of SNPs evaluated within the instruments. The beta represents the directionality of the relationship, with a positive (beta > 0) value indicating an increase in the response variable, whereas a negative (beta < 0) value indicating a decrease. A p-value < 0.05 indicates a significant correlation.

Exposure	Outcome	nSNP	Beta	P-val
BMI	B.T.	487	2.58E-01	4.02E-75
BMI	T2D	449	9.03E-01	3.57E-72
WHR	B.T.	449	9.59E-02	6.07E-12
WHR	T2D	394	5.51E-01	8.21E-27
B.T.	BMI	163	1.38E-01	1.31E-07
B.T.	WHR	163	1.04E-01	2.33E-04
B.T.	T2D	154	3.99E-01	1.92E-07
T2D	WHR	139	1.08E-01	1.82E-07
T2D	B.T.	141	7.11E-02	3.03E-14
T.T.	BMI	258	4.86E-02	2.72E-04
BMI	T.T.	487	9.98E-02	3.02E-07
WHR	T.T.	449	-8.24E-02	2.66E-06

**Table 3: Significant bioavailable and total testosterone relationships from the male dataset.** A summary of the 12 significant relationships found in the female dataset. nSNP represents the number of SNPs evaluated within the instruments. The beta represents the directionality of the relationship, with a positive (beta > 0) value indicating an increase in the response variable, whereas a negative (beta < 0) value indicating a decrease. A p-value < 0.05 indicates a significant correlation.



**Figure 2: Summary of results.** Significant relationships were found between testosterone, T2D, and obesity from bi-directional MR analysis across sex-stratified datasets. (a) Combined male-female genetic instruments; (b) male-specific instruments; (c) female-specific instruments. A blue arrow indicates that the exposure increases the response variable in the direction of the arrow; a red arrow represents a decreasing relationship. A black divider indicates bidirectionality, where there are arrowheads in both directions. “C” represents a combined dataset, “M” represents a male dataset, and “F” represents a female dataset. Combined T2D datasets were used across all three groups as depicted. Insignificant results were not depicted.

increased levels of T.T. decreased BMI. Increased BMI and WHR levels showed a significant decrease in both B.T. and T.T. These relationships suggest that male testosterone holds an antagonistic influence on disease, where obese individuals would have a lower bioavailable and total testosterone level and vice versa. Similarly, increased male T.T. decreased risk of T2D.

On the other hand, increased female testosterone concentration was associated with a significant increase in weight gain and diabetic development; both increased female T.T. and increased B.T. was correlated with a rise in BMI. Although an increase in WHR decreased T.T. levels, B.T. increased and was increased by both measurements of obesity. Furthermore, B.T. significantly increased and was increased by risk of T2D in females.

In the combined-sex dataset, the effects of total testosterone and bioavailable testosterone on disease were inversely related. As T.T. is by definition the combined measurement of bioavailable testosterone and the inactive SHBG-bound testosterone, the conflicting nature of T.T. 's negative and B.T.'s positive influence on obesity and T2D was unexpected (8). This is likely due to the confounding result presented by the use of a sex-combined dataset where the direction of effects is opposite in each gender, as testosterone in male subjects generally decreased risk and female testosterone led to a heightened risk of T2D and obesity.

Notwithstanding this discrepancy, an important finding is that while increased male testosterone is associated with beneficial outcomes towards the subject by combating obesity

and decreasing risk of T2D, increased female testosterone significantly increases the two diseases. To exacerbate matters, obesity and T2D further increase testosterone levels in women, possibly creating a positive feedback loop that may further cause the accumulation of body fat and increase blood glucose levels. A potential reason behind the sex-based physiological differences observed is polycystic ovary syndrome (PCOS) induced by the presence of high quantities of androgens such as testosterone. Insulin resistance is prevalent among 60–70% of women diagnosed with PCOS; the primary defect is believed to be an altered post-receptor signaling process (26). Insulin resistance would enhance risk of T2D, through which symptoms of obesity may be increased as well.

Therefore, while our results are in alignment with the use of testosterone replacement therapy to treat men suffering from hypogonadism and its symptoms (including obesity, T2D, as well as insufficient sperm production, muscular deficiency, and depression), they raise concerns when employing testosterone therapy for women (2). For instance, masculinizing hormone therapy is a treatment employed for transgender men (female-to-male) and nonbinary individuals who wish to produce male physiological characteristics. To minimize risks of obesity and T2D, doses of testosterone should be kept to within or below the healthy range in cis-gender males (27). Due to the potentially harmful effects of abnormal testosterone concentrations in both males and females, it also encourages an increased use of sex-stratification in testosterone analyses to avoid cross-sex



extrapolation of risk observation.

Our study has three primary limitations that should be improved upon for future work. First, as a sex-stratified dataset for T2D was unable to be located within the GWAS catalog or in previous relevant studies, our analysis resorted to utilizing the same combined T2D data across male and female-specific MR analyses. As such, the relationships between T2D and male and female-specific testosterone is less definitive. This may also explain the insignificant effect that male B.T. and female T.T. yielded on risk of T2D. As such, it is crucial to utilize sex-specific T2D genetic instruments if this study were to be replicated. Secondly, the genomic data relied on two measurements of testosterone: total and bioavailable testosterone. However, the effect of total testosterone on other variables in both males and females may be susceptible to sources of variation, as it accounts for the amount of active and inactive testosterone in an individual. The relative concentration of active bioavailable testosterone to SHBG-bound, inactive testosterone may have been a determinant of the directionality of T.T. 's relationships with obesity and T2D. Analyzing determinants for SHBG-bound testosterone – likely leading to opposite directionality from bioavailable concentration – could have strengthened the conclusions. Finally, only one form of measurement was used to predict risk of T2D: expression of relevant genes. Our findings could be further supported through analyzing gene expression for insulin resistance in pancreatic  $\beta$ -cells.

Future studies are recommended to answer the questions that have surfaced as a result of this study. For instance, while testosterone serves more homeostatic purposes for fully developed adults, one of its primary physiological purposes is the development of primary and secondary sex characteristics in both males and females. One particular area of curiosity is the effect of testosterone on obesity and T2D in developing children and adolescents; it is yet to be determined whether the conclusions of this study would be consistent across these age demographics as well. Another potential area for research is the effect of estrogen on such diseases. Although excess androgens have been shown to be protective in males and harmful in females, it is unknown whether its female sex hormone counterparts hold this relationship or its inverse. Answering such questions may help with delivering accurate clinical treatments for patients suffering from these diseases. Testosterone is a universal hormone present in humans and most other vertebrates. While most commonly associated with males as the cornerstone hormone for the development of male sex characteristics, it also serves homeostatic and sexual purposes in women (2). Given how its natural concentration declines steadily with age in both male and female humans, understanding the role that testosterone plays in regulating disease is pivotal for accurate and effective clinical administration (5,6,7). We found that testosterone yields contrasting effects on obesity and T2D in males and females: In males, increased testosterone concentration was correlated with decreased levels of such NCDs. On the other hand, testosterone was shown to significantly increase risk of obesity and T2D in females. As this study presents, sex-stratification is of utmost significance when examining testosterone's influence, and future studies that seek to do so for other common diseases are highly recommended to analyze data derived from both male and female cohorts.

## MATERIALS AND METHODS

### UK Biobank (UKBB)

Analyses were performed in the UK Biobank study (n=425,097) (22). All participants of the UKBB provided informed consent, and the study was provided ethical approval by the National Research Ethics Service Committee North West-Haydock. Total and bioavailable testosterone level instruments were selected from the database and employed our own analysis.

### DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium

The DIAGRAM data for genetic predictors of risk of T2D (n=62,892) were drawn from public databases (21). There were 12 GWAS cohorts of European descent, with roughly 2.5 million SNPs following quality control for significance.

### Genetic Investigation of Antropometric Traits (GIANT) Consortium

The GIANT Consortium is a publicly available online database for sex-stratified BMI and WHR genomic instruments (n=339,224) (23). After accounting for genomic quality control, SNPs from this dataset were implemented for analysis.

### Mendelian randomization

SNPs with significant p-values ( $p < 0.05$ ) were extracted and SNPs with high pairwise correlation ( $LP < 0.01$ ) were removed to ensure independence between included SNPs. Finally, they were harmonized prior to the MR analysis to ascertain the effects were for the same alleles.

The inverse variance weighted (IVW) model was used to calculate the causal estimate – the ratio of variant to outcome association. Furthermore, to ensure the outcome (Y) is only affected by the genetic instrument (G) through the exposure (X) – avoiding pleiotropy – the MR-Egger intercept method was implemented. A MR-Egger intercept that significantly deviates from zero would be evidence of pleiotropy, rendering the findings insignificant (20).

This process was repeated for a total of 48 times, 8 bi-directional MR analyses for each combined, male, and female group of instruments. Findings with a p-value less than 0.05 were recorded, and the sign of the IVW beta was used to determine the directionality of the relationship. All analyses were performed in the Mendelian randomization package in R.

### Data Analysis

The IVW beta, p-value, and nSNP data generated from R was collected and stored in an Excel spreadsheet. All calculations, figures, and tables were conducted and created within Google Sheets.

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