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Relationship of obesity, body fat, benign adrenal tumors and the mediating mechanism: a two-step mendelian randomization study

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Abstract

Background Benign adrenal tumors comprise the majority of asymptomatic adrenal masses and are often associated with cortisol secretion, which increases the risk of obesity and metabolic syndrome. Hormone secretion by these tumors may confound prevailing epidemiologic findings, and the causal relationships among obesity, body fat, and benign adrenal tumors remain uncertain. Mendelian randomization (MR) uses genetic variation as an instrumental variable to simulate randomized controlled trials, thereby reducing confounding and supporting causal relationships. Therefore, we aim to use MR methods to investigate causal relationships between obesity, body fat, and benign adrenal tumors. And use two-step MR to evaluate potential mediating mechanisms and their mediation proportions.

Method Single nucleotide polymorphisms significantly associated with obesity, body fat and possible mediators were selected as instrumental variables from published genome-wide association studies (GWAS). GWAS data for benign adrenal tumor cases (n = 1,790) and controls (*n* = 390,633) were obtained from the Finngen database. Univariable MR analysis was performed to evaluate the causal associations of obesity and body fat with benign adrenal tumors, with obesity and body fat quantified using ten anthropometric indicators. In addition, two-step MR was used to examine four categories of possible mediators (metabolic indicators, hormone indicators, inflammation and oxidation indicators, and diseases) to explore potential mechanisms between obesity, body fat, and benign adrenal tumors and to calculate mediation proportions.

Result Our results show that all anthropometric indicators are risk factors for benign adrenal tumors (OR range from 1.59 to 2.49 with FDR < 0.05). In addition, two-step MR analysis shows that both total and bioavailable testosterone levels significantly mediate body fat percentage, trunk fat percentage, and trunk fat mass on benign adrenal tumors in women (mediation proportion: 4.07%-15.58%). In addition, bioavailable testosterone levels mediate whole body fat mass (10.95%) and body mass index (17.04%), while total testosterone levels mediate hip circumference (7.27%) in women.

Conclusion Our study demonstrates that obesity and elevated body fat may serve as risk factors for benign adrenal tumors. Furthermore, we identify the mediating role of total/bioavailable testosterone levels in women, suggesting its potential target for prevention and intervention of benign adrenal tumors in individuals with obesity or high body fat.

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Keywords Adrenal benign tumor, Overweight, Adipose, Gonadal hormone, Metabolic syndrome, Androgens, Genetic instrumental variable

Introduction

A benign adrenal tumor is an asymptomatic lesion of the adrenal gland that is often found incidentally during imaging studies [1]. The prevalence of benign adrenal tumors ranges from approximately 4.2% to 7.3% among patients, reaching about 4–7% in individuals over 40 years of age, and up to 5–10% in those over 70 years of age [2–4]. From 1995 to 2017, the prevalence increased nearly tenfold, from 4.4 per 100,000 to 47.8 per 100,000 [5]. More than 50% of patients with benign adrenal tumors have biochemical evidence of autonomous cortisol secretion (ACS) after 1 mg dexamethasone suppression test [2]. Functional adrenal tumors, including adrenocortical adenomas, aldosterone-secreting adenomas and pheochromocytomas, may cause hormone hypersecretion, leading to serious conditions such as hypertension and hypokalemia [6, 7]. In addition, benign non-functioning adrenal tumors (NFAT) may serve as risk factors for glucose intolerance, insulin resistance, and hypertension [8]. A meta-analysis revealed that patients with both NFAT and mild autonomous cortisol excess (MACE) have an increased risk of cardiovascular metabolic comorbidities [9]. Therefore, it is necessary to clarify the risk factors of benign adrenal tumors and potentially beneficial for the early identification and targeted intervention.

Obesity, which now affects over 2 billion people worldwide representing approximately 30% of the global population [10], is strongly associated with benign adrenal tumors. Studies have shown that the prevalence of benign adrenal tumors is increased by 68–87% in obese/overweight NFAT and ACS patients compared to normal-weight participants [11]. Studies have shown that obesity may promote the development of benign adrenal tumors through insulin resistance and hyperinsulinemia [12]. In recent years, the rising incidence of benign adrenal tumors may be associated with insulin resistance, obesity, and hypertension. Although the association between benign adrenal tumors and obesity and insulin resistance has been mentioned, the specific causal relationship remains unclear [13]. In addition, several studies have shown that patients with benign adrenal tumors often have metabolic syndrome, abnormal adipokine levels, increased inflammation, and endocrine disorders [14–20]. Because of the potential bias and reverse causality caused by confounding factors in observational studies, further research is needed. To date, only studies on the gut microbiome, smoking and alcohol consumption have been published in relation to benign adrenal tumors. No studies have yet explored the role of obesity and its potential mediation effects on adrenal tumors [21, 22].

Large multicenter clinical trials can be time-consuming and costly while having limited power to infer causality. Mendelian randomization (MR) has been used to assess causal relationships between environmental exposures and outcomes using genetic variants from genome-wide association studies (GWAS) as instrumental variables (IVs) [23]. Genetic variants are randomly assigned before birth, minimizing problems of residual confounding and reverse causation that often limit observational studies. We investigated the causal relationships between obesity, body fat, and benign adrenal tumors using MR frameworks and further explored potential mediating mechanisms. Establishing conclusive causal relationships may aid in early detection and targeted interventions for patients with benign adrenal tumors.

Methods

MR design

This research is based on the summary statistics of GWAS and utilizes MR design to investigate the causal effects of obesity, and body fat on benign adrenal tumors and to explore mediators. In the choice of IVs, MR uses genetic variants as proxies for specific modifiable risk factors to estimate and test the causal effects of the outcome. The random allocation of genetic variations based on Mendel's law ensures independence from any confounding factors, thereby simulating a randomized controlled trial. The STROBE reporting guidelines were used to improve the reporting of observational epidemiologic studies (Supplementary Appendix 2, Table S1).

In this study, we first conducted univariable Mendelian Randomization (UVMR) to assess the causal relationship between obesity, body fat, and benign adrenal tumors. In addition, we examined potential mediators associated with benign adrenal tumors. Subsequently, multivariable Mendelian Randomization (MVMR) was then used to evaluate the association between potential mediators and benign adrenal tumors after adjusting for obesity and body fat. We then conducted a screening of candidate mediators in the association between obesity, body fat, and benign adrenal tumors by calculating their mediating effects. In this study, multiple assessment indicators were used to describe obesity and body fat, which increased the reliability of the results.

Data sources of exposures, mediators, and outcomes

In this MR study, all data sources are publicly available, and details of these sources are provided in Table 1. All included GWAS had obtained ethical approval from their respective institutional review boards, and informed consent was secured from participants, alongside rigorous quality control procedures. Consequently, ethical approval was not required for the present study because only summary-level data were used. Additional detailed information regarding population demographics in GWAS abstract data is presented in Supplementary Appendix 2 Supplemental text 1.

Exposure

To increase the reliability of our research, we used ten anthropometric indicators to quantify obesity and body fat. These indicators include four obesity-related indicators: body mass index (BMI), hip circumference (HC), waist circumference (WC), waist-hip-ratio (WHR) and six body fat-related indicators: body fat percentage, whole body fat mass, whole body fat-free mass, trunk fat percentage, trunk fat mass, trunk fat-free mass [24]. GWAS data for BMI were derived from a large meta-analysis of 681,275 individuals by the GIANT consortium. GWAS data for WHR, encompassing 502,773 individuals, were derived from the study by Loh et al. [25]. The remaining anthropometric measures and body fat data were obtained from the MRC-IEU consortium (whole body fat mass was based on data from the Neale laboratory due to pleiotropy of data in the MRC-IEU consortium), with full details available in Table 1. Supplementary Appendix 2 Table S2 provides the rationale for the selection of these studies.

Outcomes

Outcome: The FinnGen study is a nationwide GWAS in Finland, integrating longitudinal phenotypic data with digital health records from the national health registry system [26]. Genetic predictive factors for benign adrenal tumors were derived from the FinnGen study (https://r9.risteys.finngen.fi/endpoints/CD2_BENIGN_ADRENAL), which includes a cohort of 1,790 cases and 392,423 controls. Case diagnoses were classified according to the International Classification of Diseases, versions 8–10.

Mediators

The mechanisms between obesity and benign adrenal tumors remain controversial. Systemic low-grade inflammation, metabolic syndrome, and hormonal dysregulation are commonly implicated mechanisms in obesity-related diseases [27, 28]. After a comprehensive literature review, we identified 34 candidate mediators of benign adrenal tumors (see Table 1 for detailed information on mediators). These mediators may play a role between obesity, body fat, and benign adrenal tumors and are supported by genetic tools available from GWAS. These include metabolic indicators (fasting glucose [12, 29], fasting insulin [12, 29], insulin growth factor 1 (IGF-1) [30], insulin-like growth factor 2 (IGF-2) [31, 32], IGF-1 receptors (IGF-1R) [31, 32], systolic blood pressure [14, 33], diastolic blood pressure [14, 33], low density lipoprotein cholesterol (LDL cholesterol) level [34], total cholesterol [34], high density lipoprotein (HDL) cholesterol [35, 36], triglycerides [35, 36]), hormone indicators (estradiol level in men/women [37, 38], total testosterone level in men/women [39], bioavailable testosterone level in men/women [39], sex hormone binding globulin (SHBG) level in men/women [40], circulating leptin level [15], adiponectin level [41], resistin level [41], adrenocorticotropic hormone levels (ACTH) [42], ghrelin levels [43, 44]), inflammation and oxidation indicators (C-reactive protein (CRP) [45, 46], albumin [47], plasminogen activator inhibitor 1 (PAI-1) [34], interleukin (IL-6) [34], tumor necrosis factor α (TNF-α) [41], tumor necrosis factor receptors 1 (TNF-R1) [48], tumor necrosis factor receptors 2 (TNF-R2) [48]), diseases (type 2 diabetes (T2D) [2, 9, 29], sleeplessness/insomnia [49, 50], cognitive performance [49], COVID-19 [51], thyroid problem [17, 52, 53], esophageal cancer [54], glaucoma [55]). The relationships between IGF-2, TNF-R1, TNF-R2 and benign adrenal tumors were not investigated in this study because of a lack of established IVs. The summary data used in this study were extracted from publicly available open databases and published research, with an emphasis on data from individuals of European ancestry to reduce potential bias due to population heterogeneity. Supplementary Appendix 2 Table S2 provides the rationale for the selection of these studies.

Selection of genetic IVs

IVs were extracted from the corresponding summary level statistics to perform UVMR, MVMR, and mediation MR. In this study, the significance threshold was set at $P < 5*10-8$ to meet the relevance assumption. In addition, single nucleotide polymorphisms (SNPs) in linkage disequilibrium, $r^2 < 0.001$, in a window size of 10,000 kb were then filtered to confirm independence. In addition, filtered SNPs were further trimmed if they were palindromic or their minor allele frequencies were < 0.01. See Supplementary Appendix 1 Table S1 for details on each SNP. To reduce the bias from weak IVs, we also calculated the F-statistics of the SNPs, which represent the strength of the IVs. According to a previous study, a larger F statistic indicates stronger instrument strength, so the F statistic was used to test for weak IVs. The F-statistics of all SNPs

Table 1 Information and sources of GWAS data in exposure, mediation, and outcomes

Phenotype	No of participants	Ancestry	Consortium / cohort	Author	Year of publication	PubMed ID	Unit
Exposure							
Body mass index	681,275	European	GIANT	Yengo, L	2018	30,124,842	SD (Kg/m^2)
Waist circumference	462,166	European	MRC-IEU	Ben Elsworth	2018	NA	SD (cm)
Hip circumference	462,117	European	MRC-IEU	Ben Elsworth	2018	NA	SD (cm)
Waist-hip ratio	502,773	European	NA	Loh PR	2018	29,892,013	NA
Body fat percentage	454,633	European	MRC-IEU	Ben Elsworth	2018	NA	SD
Whole body fat mass[a]	330,762	European	Neale Lab	Neale	2017	NA	SD (kg)
Whole body fat-free mass	454,850	European	MRC-IEU	Ben Elsworth	2018	NA	SD (kg)
Trunk fat percentage	454,613	European	MRC-IEU	Ben Elsworth	2018	NA	SD
Trunk fat mass	454,588	European	MRC-IEU	Ben Elsworth	2018	NA	SD (kg)
Trunk fat-free mass	454,508	European	MRC-IEU	Ben Elsworth	2018	NA	SD (kg)
Mediators							
Metabolic Indicators							
Fasting glucose	200,622	European	NA	Chen J	2021	34,059,833	SD (mmol/l)
Fasting insulin	151,013	European	NA	Chen J	2021	34,059,833	SD (pmol/l)
Insulin growth factor 1	435,516	European	NA	Barton AR	2021	34,226,706	SD (nmol/L)
IGF-1 Receptors	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
Systolic blood pressure	810,865	European	NA	Surendran P	2020	33,230,300	SD (mmHg)
Diastolic blood pressure	810,865	European	NA	Surendran P	2020	33,230,300	SD (mmHg)
Low density lipoprotein cholesterol levels	343,621	European	UK Biobank	Neale lab	2018	NA	SD (mmol/L)
Cholesterol	344,278	European	UK Biobank	Neale lab	2018	NA	SD (mmol/L)
HDL cholesterol	315,133	European	UK Biobank	Neale lab	2018	NA	SD (mmol/L)
Triglycerides	343,992	European	UK Biobank	Neale lab	2018	NA	SD (mmol/L)
Hormone Indicators							
Estradiol levels in men	13,367 cases 134,323 controls	European	NA	Schmitz D	2021	34,255,042	Event
Estradiol levels in women	37,461 cases 126,524 controls	European	NA	Schmitz D	2021	34,255,042	Event
Total testosterone levels in men	194,453	European	NA	Ruth KS	2020	32,042,192	SD
Bioavailable testosterone levels in men	178,782	European	NA	Ruth KS	2020	32,042,192	SD
Total testosterone levels in women	230,454	European	NA	Ruth KS	2020	32,042,192	SD
Bioavailable testosterone levels in women	188,507	European	NA	Ruth KS	2020	32,042,192	SD
Sex hormone binding globulin levels in man	214,989	European	NA	Rebecca Richmond	2020	NA	SD
Sex hormone binding globulin levels in women	185,221	European	NA	Rebecca Richmond	2020	NA	SD
Circulating leptin levels	49,909	European	NA	Yaghootkar H	2020	32,917,775	SD (ng/mL)
Adiponectin levels	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
Resistin levels	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
Adrenocorticotropic hormone levels	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
Ghrelin levels	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD

Table 1 (continued)

Phenotype	No of participants	Ancestry	Consortium / cohort	Author	Year of publication	PubMed ID	Unit
Inflammation and Oxidative Indicators							
C-reactive protein	353,466	European	NA	Sakaue S	2021	34,594,039	SD (mg/L)
Albumin	432,221	European	UK Biobank	Neale lab	2018	NA	SD (g/L)
plasminogen activator inhibitor	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
IL-6	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
tumor necrosis factor α	35,559	European	deCODE	Egil Ferkingstad	2021	34,857,953	SD
Diseases							
Type 2 diabetes	61,714 cases 596,424 controls	European	NA	Xue A	2018	30,054,458	Event
Sleeplessness / insomnia	462,341	European	MRC-IEU	Ben Elsworth	2018	NA	SD
Cognitive performance	257,841	European	NA	Lee JJ	2018	30,038,396	SD
COVID-19 (hospitalized)	9,986 cases 1,877,672 controls	European	NA	COVID-19 Host Genetics Initiative	2020	32,404,885	Event
Thyroid problem (not cancer)	28,254 cases/ 456,344 controls	European	NA	Dönertaş HM	2021	33,959,723	Event
Esophageal cancer	998 cases 475,308 controls	European	NA	Sakaue S	2021	34,594,039	Event
Glaucoma	10,411 cases 474,568 controls	European	NA	Sakaue S	2021	34,594,039	Event
Outcome							
Benign neoplasm: Adrenal gland	1,790 cases 390,633 controls	European	FinnGen	NA	2022	36,653,562	Event

[a] Due to the pleiotropy of the MRC-IEU data, which cannot be adjusted by the MR-PRESSO method, Neale Lab data were used for validation

included in the MR analysis were evaluated, the formula is as follows [56]: $F = R^2 (N - k - 1) / (1 - R^2)$.

Statistical analysis and sensitivity analysis

UVMR and MVMR

We performed UVMR analyses to estimate the association between anthropometric indicators and benign adrenal tumors. In addition, we screened for potential mediators and assessed their impact on benign adrenal tumors. We also used MVMR to assess the direct effects of potential mediators on benign adrenal tumors while adjusting for anthropometric indicators to determine independent causal associations. MR assumes that: 1) the SNPs used as IVs in GWASs are associated with exposures; 2) IVs are not associated with confounders; 3) IVs influence the risk of the outcome only through exposure (Fig. 1) [23]. We use the Inverse Variance Weighted (IVW) method as the main analysis. The IVW method combines the Wald ratio estimates for each SNP into the causal estimate for each risk factor, providing robust causal estimation in the absence of pleiotropy [57]. Causality ($P < 0.05$) is conceded only if the IVW estimate is directionally and statistically significant in at least one sensitivity analysis and no compelling evidence of pleiotropy is detected. Effect sizes are reported as odds ratios (OR), beta coefficients, or proportions, with corresponding 95% CIs.

Mediation MR analysis

The statistical analysis consisted of two sequential steps. First, UVMR analysis was performed to estimate the overall causal effect (β) of genetic anthropometric indicators on benign adrenal tumors for each 1 standard deviation. In addition, we explored the relationships between potential mediators and benign adrenal tumors, followed by a detailed analysis of statistically significant mediators. In the second step, we evaluated the causal effect (β1) of anthropometric indicators on the established mediators. At the same time, we examined the reverse causal relationships between the mediators and the anthropometric indicators to ensure that the validity of the mediation model was not affected by bidirectionality. We used the MVMR technique to correct for the direct effect (β2) of the exposure variable and determined the validity of the mediation effect by calculating the causal effect (α) of the exposure factor on the mediator. The proportion of the

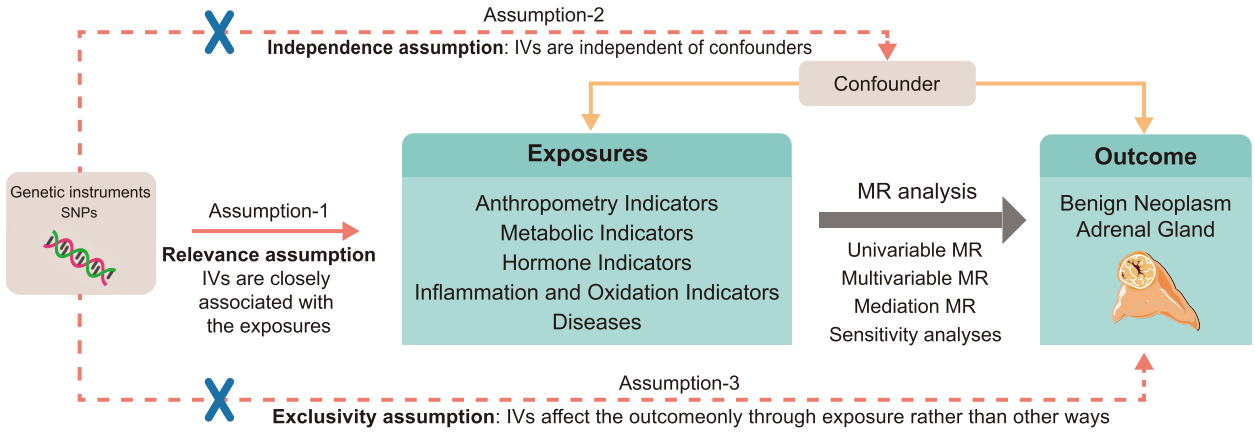

Fig. 1 The Mendelian Randomization Hypothesis: A two-sample Mendelian randomization analysis investigating five types of major mechanisms as causal factors for benign adrenal tumors. (Dashed lines represent potential causal effects between variables that may contradict the Mendelian randomization hypothesis.) Abbreviations: IV, instrumental variable; MR, Mendelian randomization

total effect of exposure on benign adrenal tumors mediated by different mediators was determined by dividing the indirect effect (α*β1) by the total effect (β). The coefficient product method was also used to calculate the percentage of the mediating effect [58]. The delta method was used to estimate the 95% confidence interval (95% CI) for the indirect effect and the proportion (Fig. 2) [59].

MR sensitivity analysis

Sensitivity analyses were conducted using MR-Egger, weighted median, weighted mode and MR robust adjusted profile score (MR.RAPS) [60]. To control for type I error rates, we performed multiple testing corrections using the Benjamini–Hochberg method. The false discovery rate (FDR) threshold was set at 0.05 to achieve significance. In addition, heterogeneity and pleiotropy are two important factors that affect the results of MR analysis. In this study, Cochran's Q test was used to assess heterogeneity. The MR-Egger regression intercept and a global test are used to quantify pleiotropy. All analyses in this study were performed with R software (version R-4.3.1). Software packages such as TwoSampleMR, MR-PRESSO, ieugwasr, MRInstruments, and forestplot, etc. were used at various stages. A significance level of $P < 0.05$ is considered indicative of significance.

Results

Total and direct effects of obesity and body fat on benign adrenal tumors

We assessed the effect of each factor on the occurrence of benign adrenal tumors using the Inverse Variance Weighted (IVW) analysis as our primary method. The influence of various factors was expressed in terms of odds ratios (OR) or beta coefficients (β) with corresponding 95% confidence intervals (95% CI). The results of false discovery rates (FDR) p-value and sensitivity analyses are shown in Supplementary Appendix 1 Table S2-S4, while scatter plots, funnel plots, and leave-one-out plots for all results are shown in Supplementary Appendix 2 Figure S1-S3. Below are the specific results for the different mechanisms.

Effect of obesity and body fat indicators on risk of benign adrenal tumors

Gene predictions show an association between increased anthropometric indicators and the risk of benign adrenal tumors, with BMI (OR = 2.01, 95% CI = 1.63–2.48); WC (OR = 2.49, 95% CI = 1.89–3.27), HC (OR = 1.73, 95% CI = 1.40–2.14), body fat percentage (OR = 2.31, 95% CI = 1.70–3.13), whole body fat mass (OR = 1.91, 95% CI = 1.79–2.86), whole body fat-free mass (OR = 1.70, 95% CI = 1.30–2.21), trunk fat percentage (OR = 1.87, 95% CI = 1.44–2.44), trunk fat mass (OR = 1.75, 95% CI = 1.41–2.18), trunk fat-free mass (OR = 1.59, 95% CI = 1.22–2.07). However, WHR showed no significant association with the risk of benign adrenal tumors ($P > 0.05$). After FDR correction, all of the above causal relationships, except for WHR, remained statistically significant. Additional estimates of MR sensitivity and FDR results are provided in Supplementary Appendix 1 Table S2. The MR-Egger intercept indicated the absence of directional pleiotropy ($P > 0.05$). Detailed results of Cochran's Q test and the MR-Egger intercept are provided in Supplementary Appendix 1 Table S3-S4. Our results indicate that different obesity assessment indicators, fat-related markers, and fat-free mass are risk factors for benign adrenal tumors (Fig. 3).

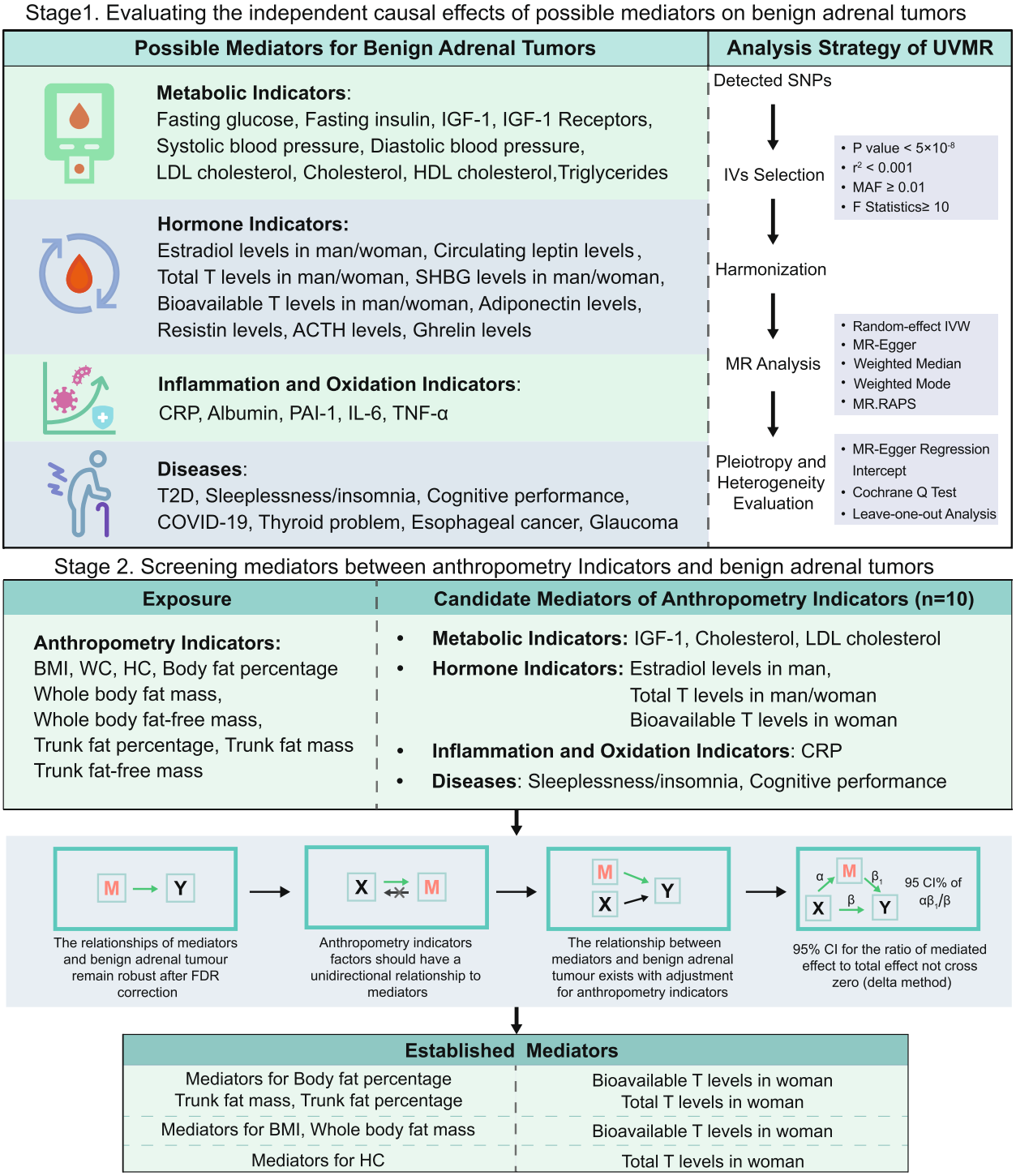

Fig. 2 Flowchart illustrating the Mendelian randomization analysis used to evaluate potential factors influencing benign adrenal tumors. Step 1 of the analysis uses UVMR to detect and identify potential risk factors contributing to the development of benign adrenal tumors. Step 2 focuses on examining obesity and body fat as primary exposures. Using MVMR techniques to elucidate potential mediating effects and underlying mechanistic pathways associated with the identified risk factors. Abbreviations: IGF-1, insulin-like growth factor 1; LDL, low density lipoprotein; HDL, high density lipoprotein; T, testosterone; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor; T2D, type 2 diabetes; IV, instrumental variable; IVW, inverse variance weighted; MR.RAPS, MR robust adjusted profile score; BMI, body mass index; WC, waist circumference; HC, hip circumference; SHGB, sex hormone binding globulin; ACTH, Adrenocorticotropic hormone; UVMR, univariable Mendelian randomization; MVMR, multivariable Mendelian Randomization

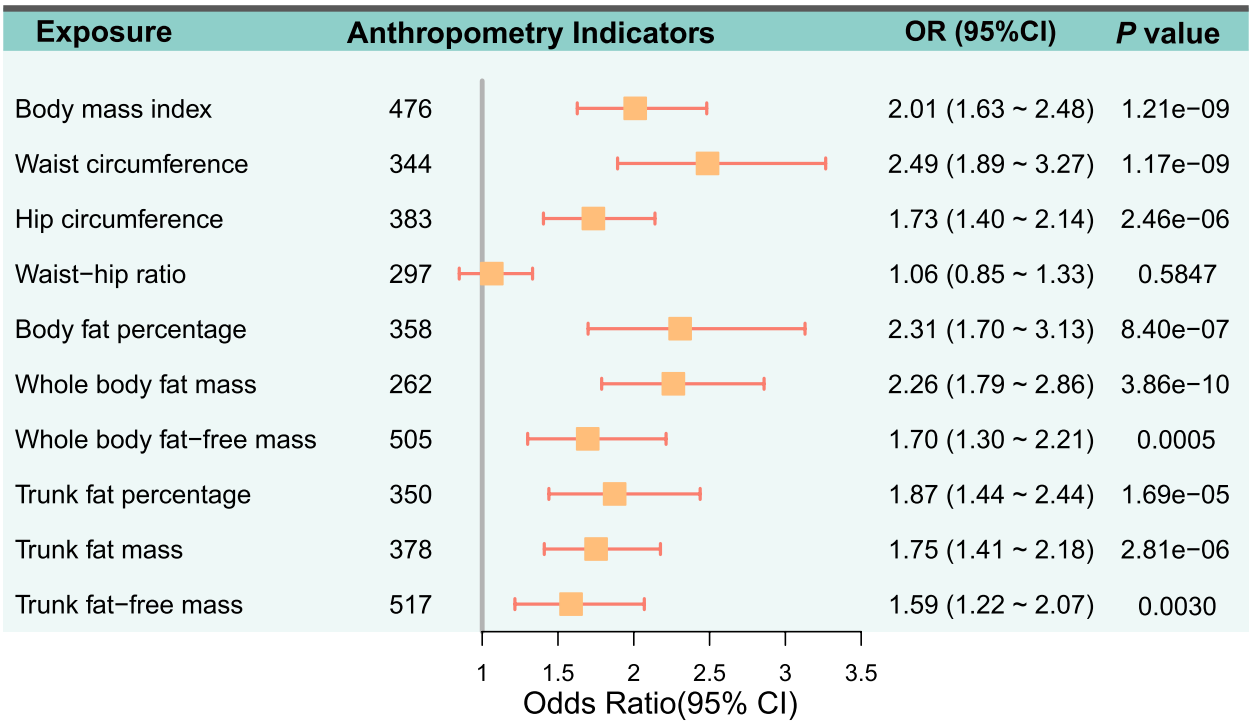

Fig. 3 Forest plot showing the causal relationship between obesity, body fat indicators, and benign adrenal tumors based on the IVW method. Abbreviations: BMI, body mass index; WC, waist circumference; HC, hip circumference; IVW, inverse variance weighted; WHR, waist-hip ratio

Effect of possible mediators on benign adrenal tumors

Based on the identification of four categories of potential mediators in relevant studies, the associations among the remaining benign adrenal tumors were examined using UVMR. The results showed a significant association: each 1-SD higher in IGF-1 (OR = 1.31, 95% CI = 1.12–1.54), estradiol level in men (OR = 1.28, 95% CI = 1.06–1.54), total testosterone level in women (OR = 1.58, 95% CI = 1.20–2.09), bioavailable testosterone level in women (OR = 1.65, 95% CI = 1.12–2.42), CRP (OR = 1.21, 95% CI = 1.01–1.46) and sleeplessness/insomnia (OR = 4.32, 95% CI = 1.35–13.83) were associated with an increased risk of benign adrenal tumors. In contrast, LDL cholesterol level (OR = 0.76, 95% CI = 0.61–0.95), cholesterol (OR = 0.81, 95% CI = 0.68–0.97), total testosterone level in men (OR = 0.81, 95% CI = 0.67–0.98), cognitive performance (OR = 0.71, 95% CI = 0.51–1.00) were associated with a decreased risk of benign adrenal tumors. After FDR correction, the associations between cholesterol, total testosterone in men, CRP, cognitive performance, and benign adrenal tumors are no longer statistically significant. Additional estimates of MR sensitivity and FDR results are provided in Supplementary Appendix 1 Table S2. The MR-Egger intercept indicated the directional pleiotropy of cholesterol (P = 0.038). Relationships between mediators and benign adrenal tumors are shown in Fig. 4 and detailed results are provided in Supplementary Appendix 1 Table S3-S4.

Therefore, in the mediation study, we selected IGF-1, LDL cholesterol levels, estradiol levels in men, total testosterone levels in women, bioavailable testosterone levels in women, and sleeplessness/insomnia as potential mediators for analysis. Mediators such as cholesterol, bioavailable testosterone levels in men, CRP and Cognitive performance were excluded due to their lack of statistical significance after FDR in the UVMR results, suggesting that these factors may not be robust mediators.

Effect of anthropometric indicators on mediators

We systematically evaluated associations between anthropometric indicators and six potential mediators, including qualified mediators in the mediation analysis. This evaluation accounted for changes in the mediators using the IVW method and further sensitivity analysis, ensuring no pleiotropy or bidirectional causation, justifying their inclusion in the mediation analysis. Each 1-SD increase in BMI (β: 0.24; 95% CI: 0.21–0.27), body fat percentage (β: 0.25; 0.20–0.30), whole body fat mass (β: 0.20; 0.16–0.23), trunk fat percentage (β: 0.17; 0.12–0.22), trunk fat mass (β: 0.17; 0.14–0.20) was associated with higher bioavailable testosterone level in women;

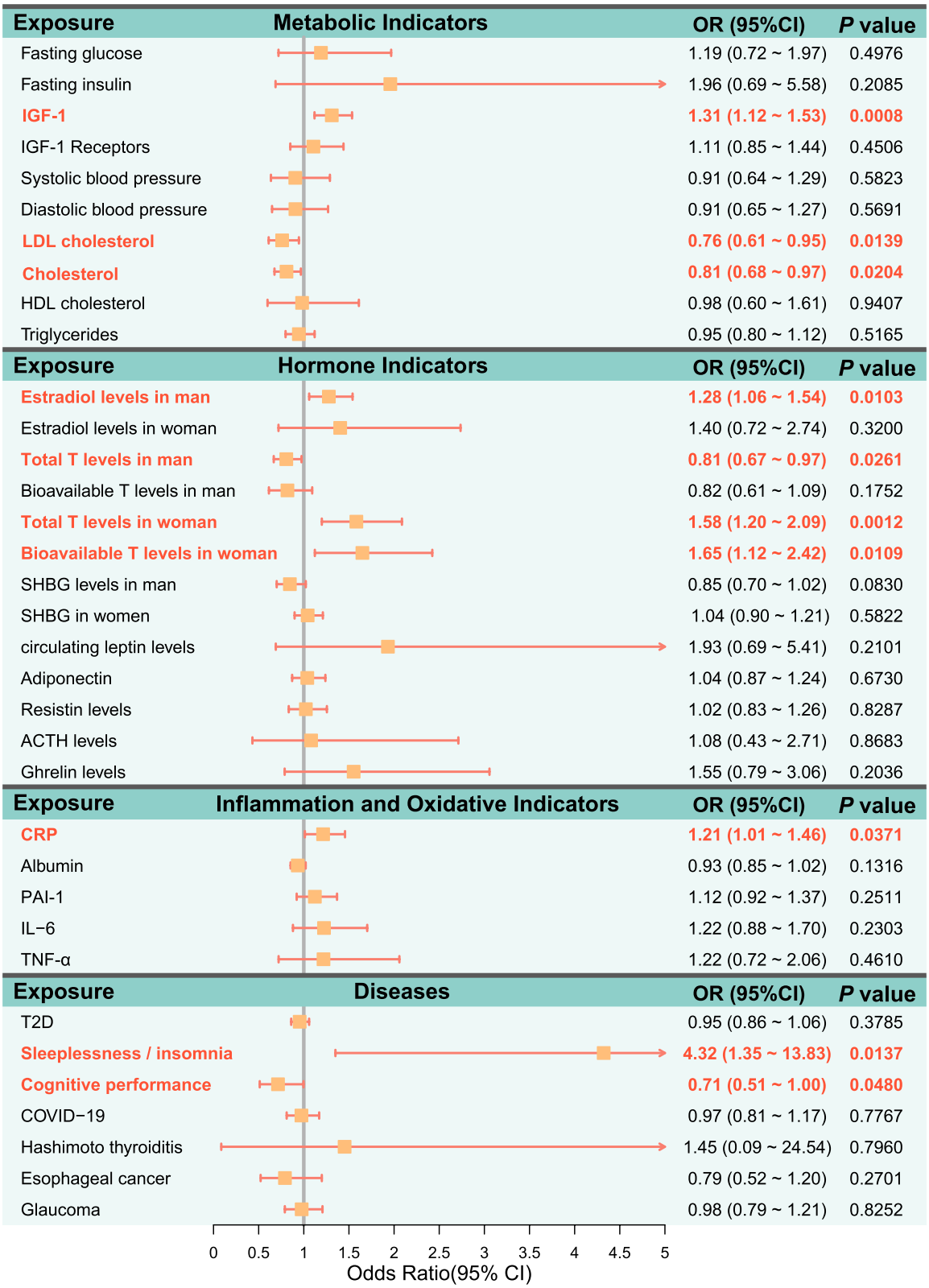

Fig. 4 Forest plot showing the causal relationship between four possible mediators and benign adrenal tumors based on the IVW method. Abbreviations: IGF-1, insulin-like growth factor 1; LDL, low density lipoprotein; HDL, high density lipoprotein; T, testosterone; SHGB, sex hormone binding globulin; ACTH, Adrenocorticotropic hormone; CRP, C-reactive protein; PAI-1, plasminogen activator inhibitor-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor; T2D, type 2 diabetes; IVW, inverse variance weighted

Each 1-SD increase in WC (β: 0.07; 0.02–0.12), HC (β: 0.10; 0.06–0.13), body fat percentage (β: 0.12; 0.07–0.18), trunk fat percentage (β: 0.09; 0.03–0.15), trunk fat mass (β: 0.07; 0.04–0.10) was associated with higher bioavailable testosterone levels in women. Each 1-SD increase in whole body fat mass (β: 0.07; 0.04–0.11) was associated with higher bioavailable testosterone level in women, whereas it was associated with lower trunk fat percentage (β: −0.09; −0.15–0.04), trunk fat mass (β: −0.09; −0.14–0.04), trunk fat-free mass (β: −0.12; −0.16–0.08). Finally, each 1-SD increase in body fat percentage was associated with higher sleeplessness/insomnia (OR: 1.06; 1.04–1.09). Detailed results are provided in Table S5, Table S8 in Supplementary Appendix 1.

Among the excluded candidate combinations, 34 were excluded due to lack of influence of anthropometric indicators (see Supplementary Appendix 1, Table S5-S7) and 7 were excluded due to bidirectional causal associations with education (see Supplementary Appendix 1, Table S8-S10).

Mediating effects of mediators in the associations of anthropometric indicators with benign adrenal tumors

In the adjustment models of the IVW analysis for individual risk factors, we further assessed the independent effect of potential mediators. To determine the direct causal effect of mediators on benign adrenal tumors, we performed a corrected MVMR analysis. MVMR shows associations of bioavailable testosterone level in women (OR: 1.68; 95% CI: 1.22–2.32), total testosterone level in women (1.50; 1.17–1.92) with body fat percentage corrected; bioavailable testosterone level in women (1. 79; 1.30–2.46), total testosterone level in women (1.46; 1.04–2.06) with trunk fat percentage corrected; bioavailable testosterone level in women (1. 58; 1.14–2.18), total testosterone level in women (1.41; 1.11–1.79) with trunk fat mass corrected; bioavailable testosterone level in women (1.64; 1.11–2.42) with BMI corrected; total testosterone level in women (1. 52; 1.22–1.90) with HC corrected; Total testosterone level in women (1.41; 1.11–1.80) with HC corrected; Bioavailable testosterone level in women with whole body fat mass corrected (1.57; 1.14–2.16). The results of the MVMR are shown in Supplementary Appendix 1, Table S11.

The mediation analysis shows that in women, the associations between body fat percentage, trunk fat percentage, trunk fat mass and benign adrenal tumors are mediated by bioavailable testosterone and total testosterone, with a mediation proportion ranging from 4.07% to 15.58%. In addition, total testosterone level in women mediates the effect of hip circumference on benign adrenal tumors, while bioavailable testosterone level in women mediates the effects of whole body fat mass and BMI on benign adrenal tumors. For a detailed depiction of the relationships between exposure, mediator, and outcome, see Fig. 5, and Supplementary Appendix 1, Table S12.

Discussion

This study aims to use genetic variation to explore the maximum number of metabolic-related risk factors for benign adrenal tumors. Our research shows that most obesity and body fat factors may contribute to the development of benign adrenal tumors, along with IGF-1,

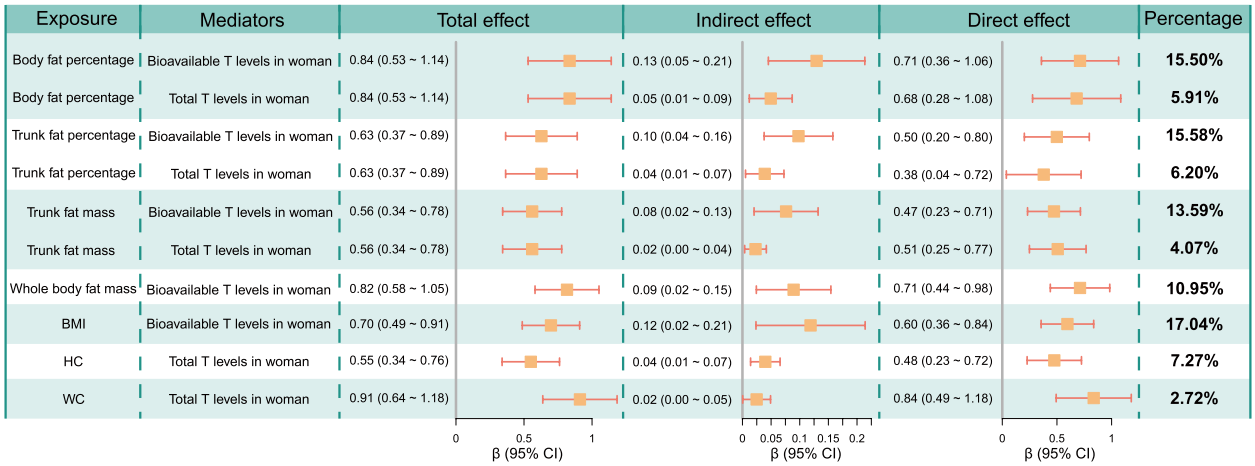

Fig. 5 The figure shows the estimated indirect effect/total effect ratio of the association between obesity/body fat and benign adrenal tumors mediated by intermediate mechanisms. The IVW Mendelian randomization method was used to estimate beta values. The proportion of the association mediated by confounders was calculated by dividing the indirect effect by the total effect. Abbreviations: T, testosterone; BMI, body mass index; WC, waist circumference; HC, hip circumference; IVW, inverse variance weighted

estradiol levels in men, total/bioavailable testosterone levels in women, CRP, and sleeplessness/insomnia. Conversely, WHR, LDL cholesterol levels, cholesterol levels, total testosterone levels in men, and cognitive performance may be protective factors for benign adrenal tumors. In addition, the evidence for causal associations between IGF-1 receptors, blood pressure, HDL cholesterol, triglycerides, adiponectin, resistin levels, albumin, PAI-1, IL-6, TNFα, SHBG level in men/women, T2D, COVID-19, thyroid problems, esophageal cancer, glaucoma and benign adrenal tumors is inconclusive, possibly due to insufficient sample size or number of SNPs and methodological limitations. MVMR and mediation analyses also elucidate the mediating role of the identified risk factors in the causal relationship between metabolic indicators and benign adrenal tumors.

Our study confirms that obesity is a significant risk factor for benign adrenal tumors and establishes causal relationships between BMI, WC, HC, and benign adrenal tumors. In observational studies, the prevalence rates of NFAT and ACS are significantly higher in the overweight/obese subgroups [11]. Approximately 20–30% of patients with adrenal tumors have clinical manifestations with varying degrees of hormonal excess, including obesity, metabolic syndrome, etc. [1, 2, 61, 62]. Due to the limited responsiveness of body composition, we also used measures of body fat indicators for validation [63]. Delivanis et al. [64] found that patients with adrenal adenomas (including NFAI) have lower muscle mass and higher levels of visceral fat. In addition, the urinary steroid profile of these patients is associated with lower lean body weight, lower bone mass, and higher visceral fat content [65]. However, some studies suggest that NFAT does not cause a significant increase in BMI or WC [66, 67]. Patients with obesity and associated comorbidities, such as those linked to metabolic syndrome, are more likely to undergo imaging studies, which could lead to an incidental diagnosis of adrenal tumors. This potential bias might influence the observed association between adrenal tumors and metabolic syndrome [68]. However, our study did not identify a significant impact of WHR on adrenal tumors. WHR is notably correlated with various metabolic indicators, including blood lipids, uric acid, blood glucose, and blood pressure [69]. Nevertheless, compared to WC and HC, central obesity has limitations, as individuals with the same WHR may have different WC and HC values [70]. In the case of adrenal tumors, the total amount of fat (such as BMI and WC) may have a greater influence than fat distribution. Further investigation requires prospective, multicenter, large-sample studies that include a broader range of clinical characteristics.

In our study, IGF-1 emerges as a potential factor in the development of benign adrenal tumors, while T2D, fasting glucose, fasting insulin, and IGF-1R lack evidence as risk factors. Some studies suggest a higher prevalence of benign adrenal tumors in patients with T2D, with tumor size correlating with insulin resistance [12], while other studies have failed to find this association [11]. T2D is associated with elevated urinary free cortisol and late-night salivary cortisol levels compared to patients without T2D [71]. IGF is a class of liver-derived mitogenic growth factors, receptors, and binding proteins involved in the normal growth, development, and differentiation of most organs and tissues, as well as in various pathological processes [72, 73]. The signaling of IGF-1 through the IGF-1R promotes the anchoring and survival of pheochromocytoma cells in the microenvironment of the murine model [74]. Elevated insulin levels stimulate the growth hormone receptor in the liver, which subsequently increases IGF-1 levels and promotes mitogenic effects in the body [75]. The causal relationship between adrenal masses and insulin resistance remains controversial [13]. Diabetes and insulin resistance may be a consequence of cortisol secretion by benign adrenal tumors rather than a causative factor. In addition, elevated levels of IGF-2 and overexpression of IGF-1R are frequently observed in benign adrenal tumors and contribute to the formation of such tumors [31, 76]. Due to the lack of GWAS data for IGF-2, the role of these molecules has not been determined.

Our study identified CRP and sleeplessness/insomnia as risk factors for benign adrenal tumors, whereas low-density lipoprotein cholesterol levels and cognitive performance may serve as protective factors. Patients with NFAT have significantly higher CRP levels than controls and are more prone to immune-related disorders such as autoimmune thyroid disease, early atherosclerosis, etc. [17, 45, 77]. However, some studies have failed to demonstrate this association [66, 78], possibly due to sample size and confounding factors. Moreover, our study identified increased insomnia and cognitive decline as potential factors associated with benign adrenal tumors. Research suggests a higher prevalence of sleep disturbances, such as insomnia, and impaired cognitive function in patients with benign adrenal tumors [49, 50]. Individuals with better cognitive abilities tend to have advantages in acquiring, comprehending and applying health information. Studies have shown that strong cognitive abilities are closely associated with social engagement, physical activity, and a healthy diet, all of which collectively enhance health literacy [79]. In one study, cognitive abilities were found to significantly mediate the effect of health literacy on the retention of knowledge regarding colorectal cancer screening, thereby playing a crucial role in preventive decision-making [80, 81]. Although no direct research has explored the role of cognitive abilities in preventing

adrenal tumors, considering the critical role of cognitive capacity in maintaining overall health, it is plausible that certain cognitive abilities may help mitigate the development of adrenal tumors. Interestingly, our study revealed that LDL cholesterol levels serve as a protective factor in benign adrenal tumors. Although some observational studies have reported elevated LDL levels in patients with benign adrenal tumors [82, 83], this discrepancy may be attributable to cortisol-induced alterations in cholesterol metabolism. For instance, Nakagawa et al. [84] found an increase in LDL receptor activity in an adrenal tumor case, which increased LDL uptake and resulted in hypolipidemia. Analysis of cortisol-producing adenoma tissue revealed that the increased cholesterol uptake and synthesis is due to the relative starvation status associated with aldosterone-producing adenomas [85]. Adrenal tissue utilizes LDL-R, SR-B1, and de novo synthesis to achieve substantial cholesterol uptake, representing the neoplastic or pathological features of autonomous steroidogenesis [85]. Therefore, lower levels of LDL cholesterol may promote the growth of benign adrenal tumors.

Furthermore, we have identified the mediating mechanisms among obesity, body fat, and benign adrenal tumors. In women, total/bioavailable testosterone levels mediated the association between obesity and benign adrenal tumors. However, within the scope of our analysis, no intermediary role has been observed in males based on the factors evaluated. Obesity is more prevalent in female populations in both developed and developing countries [86, 87]. Simultaneously, benign adrenal tumors are more common in women [9], suggesting that obesity may represent a particularly pertinent risk factor in this gender. Sex hormone differences between men and women may contribute to differences in disease prevalence, with testosterone levels potentially playing a critical intermediary role.

Our study confirms that bioavailable testosterone and total testosterone in women may mediate the promoting effect of body fat on benign adrenal tumors. Indran et al. [88] estimated that 25% of testosterone in women is produced by the ovaries, 25% by the adrenal glands, and the remaining 50% by peripheral tissues. In adolescent girls, excess fat promotes androgen production and peripheral conversion of androstenedione to testosterone in adipose tissue, resulting in increased free testosterone [89, 90]. Perimenopausal and postmenopausal women have elevated testosterone levels associated with increased body fat [91, 92]. There is an association between elevated androgens and obesity in women. Serum androgens are associated with the risk of obesity and metabolic syndrome/type 2 diabetes [93]. MR studies have validated the association of testosterone with insulin resistance and obesity [94, 95]. Studies suggest that obesity may be a major contributor to high androgenic anovulation, particularly in the absence of adrenal sources of excess androgens [96, 97]. After weight loss measures, the condition of hyperandrogenemia can be alleviated. Following weight loss surgery or exercise, testosterone levels decrease significantly in severely obese women [98, 99]. Enzymes involved in the de novo synthesis or alternative pathways of androgens, such as StAR, CYP11A1, LH receptors, AKR1C2, and AKR1C3, are elevated to varying degrees in the adipose tissue of obese individuals [100, 101]. Wagner, Savchuk [101] found that the capacity for steroidogenesis and androgen biosynthesis is increased in adipose tissue and adipocytes. This increased activity may contribute to hyperandrogenemia in obese women.

In women, the synthesis of testosterone precursors occurs primarily through biosynthesis in the adrenal cortex and ovaries, with subsequent conversion to testosterone in the periphery. Adrenal androgens are secreted into the peripheral androgen pool and are converted to both active and inactive androgens [102]. Elevated androgenemia is often associated with changes in ovarian or adrenal history, but the causal relationship remains unclear [103, 104]. Gourgari et al. [105] found that 92.5% of women with typical hyperandrogenemia associated with polycystic ovary syndrome (PCOS) and 40% of those with atypical PCOS failed to achieve complete suppression of their testosterone levels after using dexamethasone. In addition, in the overweight subgroup (BMI > 25), there was a positive correlation between BMI and both adrenal volumes, suggesting that the etiology of unexplained hyperandrogenemia may be partly related to obesity [105]. In men, there is a trend toward a protective effect of total testosterone (Total testosterone) levels against benign adrenal tumors. Studies have suggested that androgens may exert a direct inhibitory effect on benign adrenal tumor growth by activating androgen receptors and suppressing the WNT/β-catenin signaling pathway [106].

While testosterone may mediate the relationship between obesity and benign adrenal tumors, its importance in mediating fat-free body weight is not supported. This suggests that the influence of non-fat tissue may not be a critical factor affecting testosterone levels. Therefore, our study used MR methods to tentatively identify the pathogenic mechanisms of benign adrenal tumors in women.

To our knowledge, the strength of this study lies in the novel use of UVMR and MVMR analyses to investigate risk factors for benign adrenal tumors and to explore potential mediating effects. Compared with observational studies, this analytical approach is less susceptible to confounding, reverse causation, and non-differential measurement error in exposures [107]. The robustness of the IVW estimates in this study was supported by several

MR sensitivity analyses, each incorporating different assumptions regarding genetic pleiotropy. In addition, we used the FinnGen study, which has minimal overlap with exposures or mediators in the GWAS, to ensure a low type 1 error rate.

This study has several limitations. First, benign adrenal tumors include cortisol-secreting adenomas, aldosterone-secreting adenomas, pheochromocytomas, NFAT, etc. [108]. This heterogeneity in etiology and clinical diagnosis may affect the statistical power of genetic variation. Despite using the largest current adrenal benign tumor GWAS, the relatively low case rate in the FinnGen dataset may lead to reduced statistical power for certain types. In the absence of large-scale GWAS data for specific traits and molecules, including IGF-2, IGF-1R aromatase, homeostasis model assessment of insulin resistance, cortisol, epinephrine, and other related factors, several relationships remain unvalidated. Future studies should consider using larger sample sizes for further validation. Second, due to privacy restrictions on personal information, we were not able to determine sex differences in a larger population or the effect of other demographic factors. The GWAS included in this study predominantly included individuals of European ancestry, which mitigates population stratification bias, but partially limits the generalizability of the findings. The conclusions need to be further validated in other populations. Third, when examining mediating effects, the sample overlap used to assess genetic associations between exposures and outcomes could introduce a weak instrumental bias into the MR analyses. Finally, this study relies on aggregate-level statistics. This precludes the exploration of non-linear relationships between modifiable factors and benign adrenal tumors and non-linear relationships with disease severity. In conclusion, these findings should be interpreted with caution and require further validation in other studies.

Conclusions

Our MR analysis supports the proposition that obesity (as indicated by BMI, WC, HC), body fat (as indicated by body fat percentage, whole body fat mass, trunk fat percentage, trunk fat mass), and fat-free mass (as indicated by whole body fat-free mass, trunk fat-free mass) may all potentially promote the growth of benign adrenal tumors. In addition, factors such as IGF-1, estradiol levels in men, total and bioavailable testosterone levels in women, and sleeplessness/insomnia are emerging as potential risk factors for benign adrenal tumors. Conversely, LDL cholesterol levels, total testosterone levels in men, and cognitive performance have been suggested as potential protective factors against benign adrenal tumors. Simultaneously, we have constructed a mediation model to elucidate the testosterone-mediated effect of obesity on benign adrenal tumors in women. Finally, it is advisable to use multiple indices to evaluate individuals with obesity, coupled with the monitoring of metabolic indicators, sex hormone levels, and diseases. This comprehensive approach should include screening and surveillance of high-risk patients, thereby contributing to the prevention of benign adrenal tumors.

Abbreviations

ACS	Autonomous cortisol secretion
NFAT	Non-functioning adrenal tumors
MACE	Mild autonomous cortisol excess
BMI	Body mass index
MR	Mendelian randomization
GWAS	Genome-wide association studies
IV	Instrumental variable
UVMR	Univariable Mendelian Randomization
MVMR	Multivariable Mendelian Randomization
WC	Waist circumference
HC	Hip circumference
IGF-1	Insulin-like growth factor 1
IGF-2	Insulin-like growth factor 2
IGF-1R	IGF-1 receptors
LDL	Low density lipoprotein
HDL	High density lipoprotein
T	Testosterone
CRP	C-reactive protein
PAI-1	Plasminogen activator inhibitor-1
IL-6	Interleukin-6
TNF-α	Tumor necrosis factor
TNF-R1	Tumor necrosis factor receptors 1
TNF-R2	Tumor necrosis factor receptors 2
T2D	Type 2 diabetes
SNP	Single nucleotide polymorphisms
IVW	Inverse variance weighted
MR.RAPS	MR robust adjusted profile score
FDR	False discovery rates
ACTH	Adrenocorticotropic hormone
SHBG	Sex hormone binding globulin levels
WHR	Waist-to-Hip Ratio

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

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Authors' contributions

W.S. and Q.W. contributed to the conception and design of the study. Q.W. and J.W. wrote the paper. D.L. and M.J. collected and analyzed the data. H.Z. and J.L. drafted and revised important sections of the tables or figures. J.L. and H.D. performed the statistical analysis. W.S. and D.L. provided comments and revisions to the manuscript and revised and edited the text. All authors reviewed and approved the final manuscript for publication.

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Data availability
All data used in this study consist of publicly available summary-level information, and relevant details from GWAS are provided in the Supplementary Appendix. Some of these data can be found in published articles (PubMed IDs are provided in Table 1). In particular, data from the Integrative Epidemiology Unit (IEU) can be obtained from the official website (https://gwas.mrcieu.ac.uk/). R9 data from the FinnGen database can be accessed via the website (https://r9.risteys.finngen.fi/endpoints/CD2_BENIGN_ADRENAL). Access to protein data from the deCODE database can be requested from the website (https://www.decode.com/summarydata/).

Declarations

Ethics approval and consent to participate
All participants in the original genome-wide association study provided informed consent. Ethical review and approval for the GWAS dataset can be accessed in the original study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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