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Original Article

Unraveling the genetic basis of metabolic traits and benign adrenal tumors: a comprehensive causal analysis

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Abstract: Objective: Cardiovascular and metabolic diseases, including both obesity and blood pressure, have been previously implicated in observational studies as having some association with the occurrence of adrenal tumors. This study aims to evaluate the causal relationships of these high-risk factors with the disease using a Mendelian randomization approach with two-sample data. Single nucleotide polymorphisms (SNPs) for blood pressure, body mass index (BMI), blood glucose, and cardiovascular diseases were extracted from publicly available whole-genome databases. They were then compared separately with benign adrenal tumors. It was found that only BMI was associated with the occurrence of benign adrenal tumors, and this process may be mediated by C-reactive protein (CRP). We explored whether C-reactive protein (CRP) can mediate the causal relationship between body mass index (BMI) and benign adrenal tumors, further investigating the mechanism and the proportion of CRP involved in this process. Methods: Utilizing a two-sample Mendelian randomization approach, comparisons were made between BMI, blood pressure, cardiovascular diseases, blood glucose, and the outcome. Subsequently, both two-sample Mendelian randomization and multivariable Mendelian randomization (MVMR) analyses were conducted to investigate whether CRP serves as a mediator in the causal relationship between BMI and benign adrenal tumors, while calculating the proportion of mediation involved. Results: There was no causal relationship observed between blood pressure (OR = 0.976, 95% CI = 0.931-1.024, P = 0.339), blood glucose (OR = 0.960, 95% CI = 0.648-1.422, P = 0.840), cardiovascular diseases (OR = 0.724, 95% CI = 0.244-2.142, P = 0.559), and benign adrenal tumors. However, a positive causal relationship was found between BMI and benign adrenal tumors (OR = 1.20, 95% CI = 1.06-1.35, P = 0.003). There was also a positive causal relationship observed between BMI and CRP (OR = 1.07, 95% CI = 1.06-1.08, P < 0.01), as well as between CRP and benign adrenal tumors (OR = 1.350, 95% CI = 1.058-1.722, P = 0.001). After adjusting for CRP, the causal relationship between BMI and benign adrenal tumors diminished (OR = 1.044, 95% CI = 0.911-1.970, P = 0.067). Even after controlling for BMI, a causal relationship between CRP and benign adrenal tumors persisted (OR = 1.32, 95% CI = 1.035-1.693, P = 0.025). The proportion of mediation by CRP was calculated to be 10.4%. Conclusion: Using Mendelian genetic research methods, this study provides evidence that elevated levels of C-reactive protein may serve as a crucial mediating factor in BMI-induced benign adrenal tumors. Therefore, clinicians should pay particular attention to monitoring and managing levels of C-reactive protein when dealing with obese patients, to more effectively prevent the development of adrenal tumors.

Keywords: Mendelian randomization, benign adrenal tumors, C-reactive protein

Introduction

Obesity, abnormal blood glucose levels, cardiovascular diseases, and hypertension have become global public health concerns. These pathological states not only affect overall metabolic function but may also be associated with the development of various diseases. Body

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mass index (BMI), as a crucial indicator of obesity, has been linked to increased adrenal volume, affecting metabolism, and associated with various chronic diseases [1]. Abnormal blood glucose levels can lead to diabetes, causing systemic endocrine imbalance and metabolic disorders, potentially affecting hormonal balance and metabolic pathways [2]. Cardiovascular diseases, as one of the leading causes of global mortality, are worth noting in their relationship with chronic inflammation and oxidative stress. Additionally, hypertension, as a significant component of cardiovascular diseases, may indirectly affect adrenal health by influencing adrenal hormone secretion [3, 4]. C-reactive protein has been shown to be closely related to various metabolic diseases in several studies [5]. Benign adrenal tumors, as a relatively common adrenal disease, may have mechanisms of occurrence related to the aforementioned factors. However, there is currently a lack of clear scientific evidence regarding the specific relationship between these high-risk factors and benign adrenal tumors.

Benign adrenal tumors are non-cancerous growths that form in the adrenal glands. As part of the endocrine system, the hormones secreted by the adrenal glands can act on various organs and tissues throughout the body. Over the past 20 years, with the development of high-resolution radiological imaging, our understanding of adrenal diseases has significantly improved [6]. Epidemiological statistics indicate that the majority of adrenal tumors are benign, with only 5-8% being malignant. Whether benign or malignant, most of these lesions are associated with excess adrenal hormone production, including cortisol, aldosterone, and catecholamines [7, 8]. Although most benign adrenal tumors do not cause symptoms, prolonged and persistent high levels of hormone secretion can lead to a range of adverse symptoms and even life-threatening conditions. For instance, elevated levels of circulating catecholamines and increased blood pressure can result in sustained or episodic hypertension, severe headaches, palpitations, and increased sweating due to excessive hormone secretion. Failure to diagnose or treat these conditions promptly may pose a significant threat to one's life [9]. The etiology of these diseases is not well understood, but current research suggests a link with genetics and metabolism. Therefore, identifying the etiology of these diseases is crucial for primary prevention of benign adrenal tumors.

Research has found that the levels of C-reactive protein (CRP) in benign adrenal tumors are increased compared to the normal group [10]. CRP is an important biomarker of inflammation and plays a crucial role in both acute and chronic inflammatory responses. Primarily produced by the liver, its levels can rise in response to inflammatory stimuli [11]. The inflammatory process is activated in the early stages of fat growth and in chronic obesity, skewing the systemic immune response towards a perpetually pro-inflammatory phenotype [12]. Many key inflammatory markers have long been associated with obesity and obesity-related diseases, and current research supports the notion that CRP levels are typically higher in obese patients [13, 14]. Overall, the presence of persistent inflammation in obese individuals is undeniable. Immune response and metabolic regulation are highly integrated in the body, with their normal functions dependent on each other. However, if this balance is disrupted, it can lead to a series of inflammatory and metabolic disorders [13]. As an endocrine organ in the body, the adrenal gland is to some extent affected by this inflammation and metabolic disruption. Additionally, research has shown a close association between obesity and tumor development, with adrenal tumors being the most common endocrine tumors in obesity-induced tumors, posing the highest risk. However, the relationship between BMI, CRP, and benign adrenal tumors is still unclear, thus we speculate that BMI may have a positive causal relationship with benign adrenal tumors through the mediation of CRP. However, this potential mediating effect is uncertain, so further investigation with additional tools is needed to confirm it.

When exploring the causal relationship between body mass index (BMI) and benign adrenal tumors, Mendelian randomization (MR) provides a robust methodological framework. Unlike traditional cross-sectional studies, the MR method can utilize genetic variation as instrumental variables, thereby reducing the impact of confounding factors and providing more reliable evidence of causality. Our study employs a two-sample MR approach, which is particularly

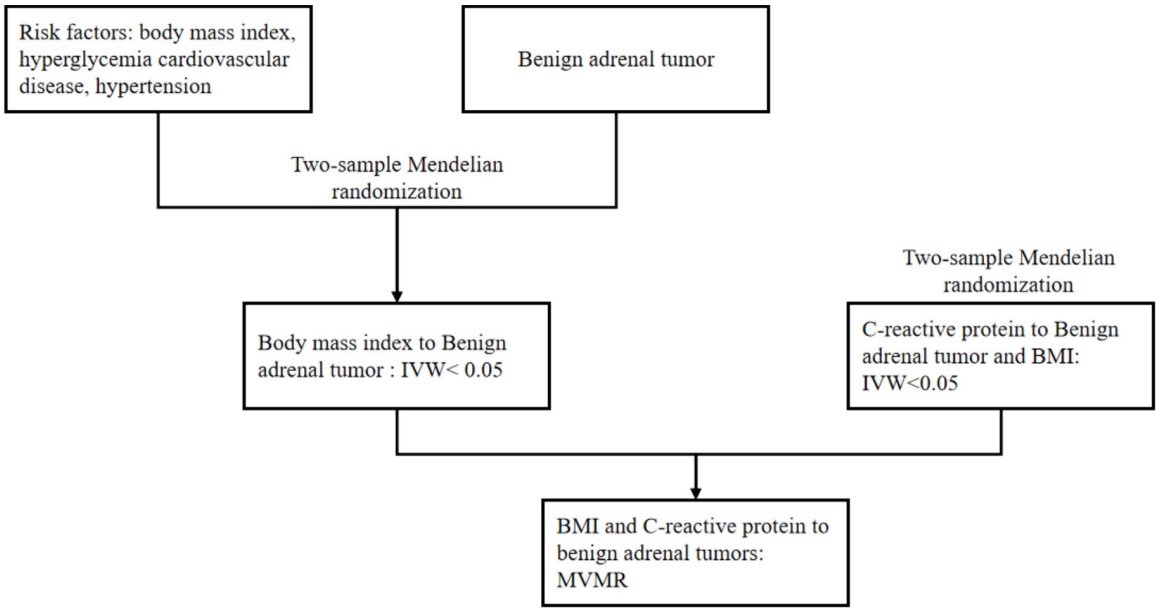

Figure 1. Finding and estimating the mediating process of CRP in BMI and BC using MVMR. The diagram illustrates two-sample Mendelian randomization analyses assessing the causal effects of various risk factors, including BMI and C-reactive protein, on benign adrenal tumors, with significant associations (IVW < 0.05) followed by multivariable Mendelian randomization to evaluate their combined effects.

suitable for our research scenario because our exposure variable (BMI), potential mediator variable (CRP), and outcome variable (benign adrenal tumors) data are derived from different databases. This separation of data sources provides us with a unique opportunity to assess the complex relationships among these variables in a larger sample, significantly improving statistical power, analytical accuracy, and avoiding false-positive results [15, 16].

The two-sample Mendelian randomization (MR) method requires the selected genetic variants to meet three key conditions: association with the risk factor (the relevance assumption), independence from the outcome (the independence assumption), and influencing the outcome only through the risk factor (the exclusion restriction assumption) [17, 18]. Based on these criteria, we chose relevant genetic variants as instrumental variables to explore the potential causal relationship between BMI and benign adrenal tumors. Furthermore, by examining the relationship between BMI and CRP, we further assessed the possibility of CRP serving as a potential mediator. The application of this research method, especially in exploring complex causal relationships, provides us with a more in-depth research approach.

Materials and methods

Study design

In our study, we initially utilized a two-sample Mendelian randomization (MR) method to investigate the causal effects of four high-risk factors (hypertension, high body weight, high blood glucose, and cardiovascular diseases) on benign adrenal tumors. Subsequently, we found a significant causal relationship between BMI and benign adrenal tumors (IVW < 0.05). We then further explored the relationship between BMI, CRP, and benign adrenal tumors. Through two-sample Mendelian randomization analysis, we investigated the potential causal mediating role of CRP between BMI and benign adrenal tumors. Additionally, by employing the multivariable Mendelian randomization (MVMR) technique, we were able to more accurately control for various confounding factors, thereby accurately estimating the proportion of mediation effect of CRP on the relationship between BMI and benign adrenal tumors (See **Figure 1**).

Data sources and statistical analysis

Data on cardiovascular diseases were obtained from the EBI database, with a total sample size of 477,807. Blood pressure data were also

sourced from the EBI database, comprising 400,458 samples. Blood glucose data were sourced from the IEU database, with a sample size of 97,656. Genetic data relevant to BMI were obtained from the UKB database, with a sample size of 454,884. CRP-related data were sourced from the EBI database, totaling 353,466 samples [19]. Data on benign adrenal tumors were sourced from the Finnish database, which included 725 cases and compared with 218,067 Europeans (**Table 1**). All studied populations were of European origin, aiming to minimize potential biases due to population heterogeneity. No additional ethical declaration or consent was required for this study. All data were retrieved from the website https://gwas.mrcieu.ac.uk/.

Selection of genetic instrumental variables

In Mendelian randomization (MR) studies, the selection of genetic instrumental variables is guided by three core assumptions. We identify suitable single nucleotide polymorphisms (SNPs) across the entire genome, with a significance threshold of P < 5×10^-8, ensuring their independence (r^2 threshold < 0.001; kb > 10,000 kb). SNPs directly influencing the outcome variable are excluded. Additionally, incompatible allele genes and palindromic sequences are removed by referencing exposure and outcome databases. The final instrumental variables are determined, followed by the calculation of the F statistic for each SNP (F = β^2/se^2), where β represents the effect of the SNP on the exposure and se is the standard error. To ensure analytical accuracy, typically only SNPs with an F statistic greater than 10 are used as instrumental variables, thereby minimizing bias due to weak instruments [20].

Selection of genetic instrumental methods and sensitivity analysis

To validate causal relationships, this study employed various analytical methods, including Inverse Variance Weighting (IVW), weighted median method, and MR Egger regression. The IVW method was primarily relied upon for MR analysis, while sensitivity analyses were conducted to assess potential pleiotropy and heterogeneity in MR estimates. The intercept of MR Egger regression was used to assess horizontal pleiotropy, while Cochran's Q test was employed to detect heterogeneity among different genetic variants. Furthermore, stability of results was ensured through leave-one-out analysis, wherein each single nucleotide polymorphism (SNP) was removed one at a time for reanalysis. All MR analyses were conducted using R language (version 4.3.1) and TwoSampleMR package (version 0.6.1) [21]. In situations where randomized controlled trials (RCTs) were not feasible, MR methods using SNPs as instrumental variables (IVs) served as an effective alternative strategy for inferring causal relationships between exposure and outcomes [22].

Calculation of mediation effects

Initially, MR with two samples was utilized to compute the value of BMI to CRP (b1). Subsequently, multivariable Mendelian randomization (MVMR) was employed to control for BMI, and the value of CRP to benign adrenal tumors (b2) was computed. Finally, the total effect value of BMI to BC (b3) was calculated, utilizing the mediation effect formula = b1×b2/b3 [23].

Results

We conducted two-sample MR analyses, using observational studies on BMI, blood sugar, cardiovascular diseases, and blood pressure as exposures for high-risk factors, and examined their associations with outcomes. SNPs with a significance level of P < 5×10-8 were extracted and excluded SNPs (r^2 ≥ 0.001, clumping window ≤ 10,000 kb). From the results, we found that only BMI showed a positive causal relationship with the outcome, whereas blood sugar (OR = 0.960, 95% CI = 0.648-1.422, P = 0.840), cardiovascular diseases (OR = 0.724, 95% CI = 0.244-2.142, P = 0.559), and blood pressure (OR = 0.976, 95% CI = 0.931-1.025, P = 0.340) showed no causal relationship (**Table 2**).

We further conducted MVMR analysis to examine whether CRP mediates the relationship between BMI and benign adrenal tumors (**Figures 3**-**5**). When controlling for BMI, CRP still exhibited a causal relationship with benign adrenal tumors (OR = 1.323, 95% CI = 1.035-1.693, P = 0.025). However, when controlling for CRP, the causal relationship between BMI and benign adrenal tumors was no longer significant (OR = 1.044, 95% CI = 0.911-1.197, P = 0.530). Through MVMR analysis, we found that after controlling for CRP, BMI became non-sig-

Table 1. Summary of the GWAS included in this MR study neoplasms

Exposure/Outcome	Gwas id	Sex	Race	Sample Size	Single Nucleotide Polymorphism (SNP)	Authors	year
Body mass index	ieu-b-4816	Males and Females	European	99,998	7,191,606	Howe LJ	2022
C-reactive protein	ebi-a-GCST90029070	Males and Females	European	575,531	10,713,245	Said S	2022
Benign adrenal tumor	finn-b-CD2_ BENIGN_ ADRENAL	Males and Females	European	Ncase: 725 Ncontrol: 218,067	16,380,466	NA	2021
Cardiovascular disease	ebi-a-GCST90029019	Males and Females	European	477,807	11,973,400	Loh PR	2018
Systolic blood pressure	ieu-b-4818	Males and Females	European	97,656	8,029,645	Howe LJ	2022
Blood glucose levels	ebi-a-GCST90025986	Males and Females	European	400,458	4,218,897	Barton AR	2021

Table 2. Mendelian randomization analysis of four risk factors

Method	SNP	Heterogeneity statistics	Horizontal pleiotropy	IVW(P)
BMI - disease	35	0.713	0.872	0.003
Cardiovascular disease - disease	215	0.108	0.064	0.560
Blood sugar - disease	112	0.571	0.297	0.840
Blood pressure - disease	20	0.613	0.146	0.340

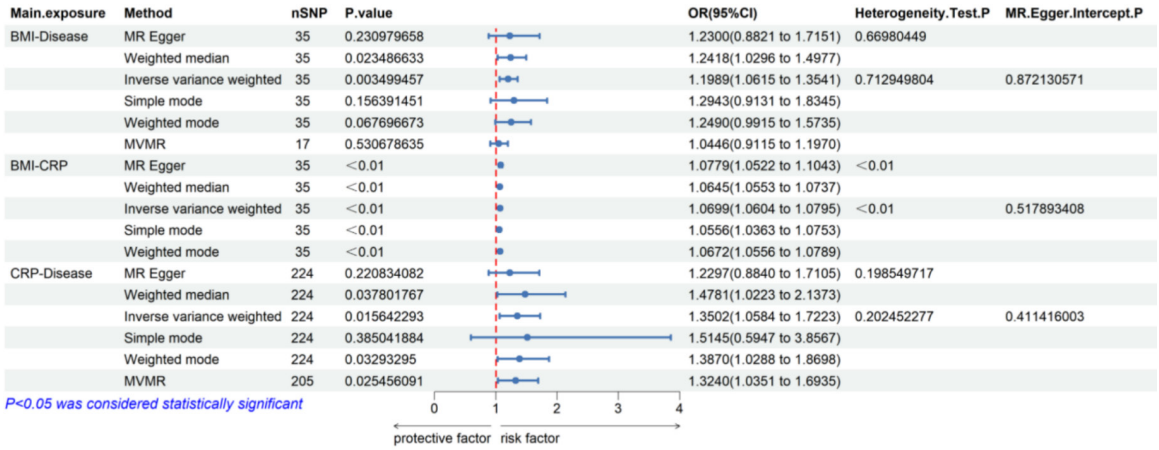

Figure 2. Two-sample and multivariable Mendelian randomization results. This figure presents the results of two-sample and multivariable Mendelian randomization analyses evaluating the causal relationships between BMI, C-reactive protein (CRP), and benign adrenal tumors using various MR methods. Odds ratios (ORs) with 95% confidence intervals (CIs) are shown, with *p*-values < 0.05 considered statistically significant. The x-axis indicates whether the factor is protective or a risk factor.

nificant in relation to the outcome, indicating that CRP likely mediates this causal effect (see **Figure 2**). The calculated mediation effect according to the formula = b1×b2/b3 was 10.4% (OR = 1.019, 95% CI = 1.002-1.037).

Discussion

With the development of society, the population of obese individuals is growing rapidly, to the extent that it is now considered an epidemic. CRP, as a biomarker of inflammation, is also considered a key factor in metabolic disorders and tumors. Through MR, we explored the associations between BMI, CRP, and benign adrenal tumors, particularly investigating the impact of BMI on benign adrenal tumors mediated by CRP.

Firstly, we found a strong positive causal relationship between BMI and CRP. This result supports the idea that obesity induces systemic inflammation, as reflected by elevated CRP levels. Inflammation plays a crucial role in metabolic disorders, and our findings align with previous studies suggesting that chronic low-grade inflammation in obese individuals may contribute to various diseases, including benign adrenal tumors. Theoretically, elevated CRP levels suggest the presence of some form of inflammation in the body, and low-grade chronic inflammation is a characteristic feature of obesity [24]. Conversely, research has also demonstrated that obesity is one of the determining factors for low-grade chronic inflammation in the general population [25]. CRP is believed to be expressed in adipocytes, as structural and metabolic changes in adipocytes make them more susceptible to hypoxic injury and rupture, leading to the release of pro-inflammatory adipokines such as IL-6, IFN-γ, and TNF-α. These pro-inflammatory mediators are elevated in obese individuals [26, 27]. Increased levels of these inflammatory factors, such as IL-6, can stimulate the liver to release CRP [28]. Furthermore, we found that CRP was significantly associated with benign adrenal tumors. This suggests that CRP, a key inflammatory marker, may play a role in the pathogenesis of benign adrenal tumors. Elevated CRP levels are commonly observed in patients with metabolic diseases, and our results indicate that CRP may mediate the relationship between obesity and adrenal tumor formation. Studies have shown that patients with pheochromocytomas acquire the ability to produce IL-6 over time, and IL-6 can promote the release of CRP by the liver. Another study demonstrated that CRP levels in patients with benign adrenal tumors are significantly higher than normal levels, and after tumor resection, CRP levels decrease by 50% [29-31]. Additionally, there is a complex relationship between aldosterone tumors, pheochromocytomas, hormone secretion in the body, and the regulation of CRP. For example, research has indicated that patients with aldosterone tumors have higher levels of IL-6 and tumor necrosis

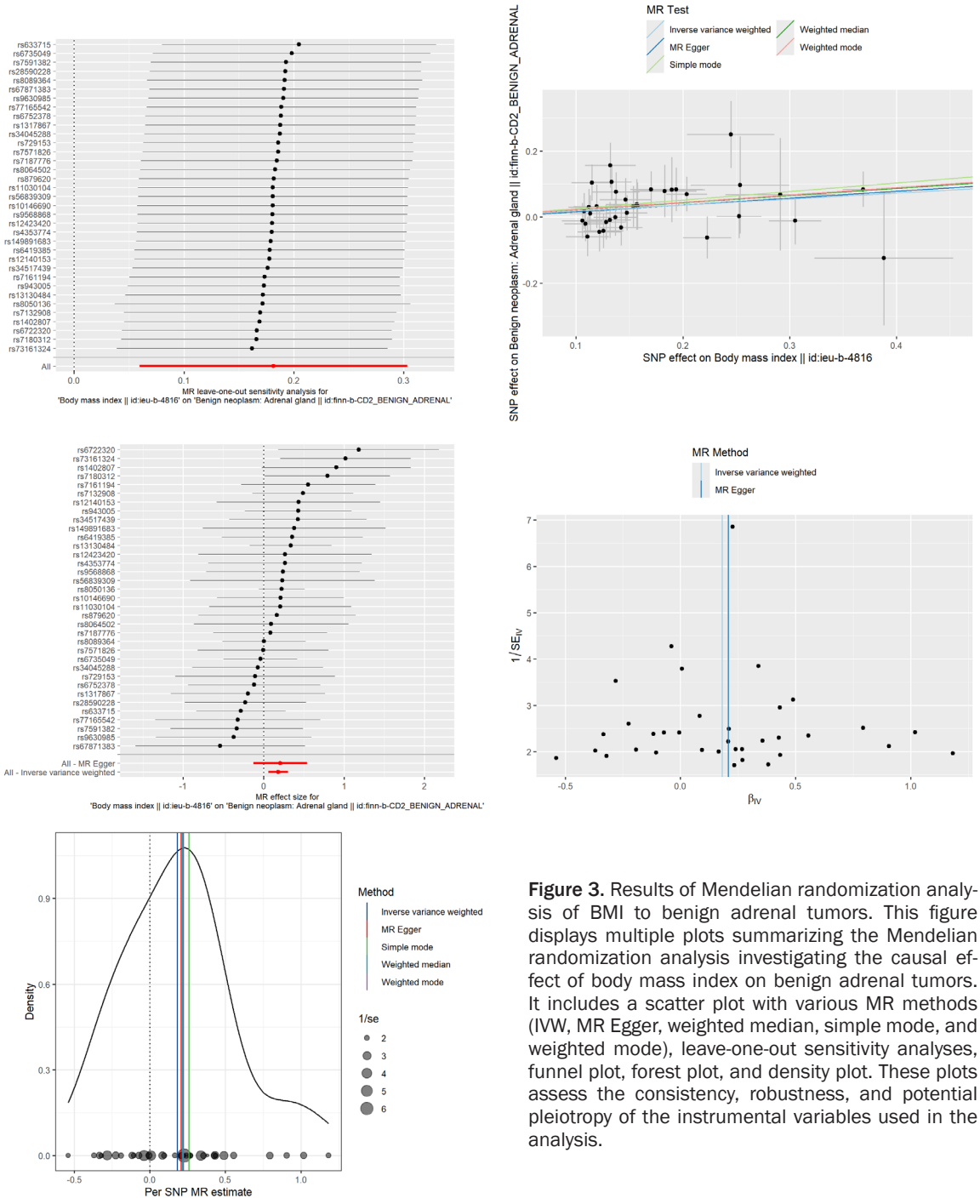

Figure 3. Results of Mendelian randomization analysis of BMI to benign adrenal tumors. This figure displays multiple plots summarizing the Mendelian randomization analysis investigating the causal effect of body mass index on benign adrenal tumors. It includes a scatter plot with various MR methods (IVW, MR Egger, weighted median, simple mode, and weighted mode), leave-one-out sensitivity analyses, funnel plot, forest plot, and density plot. These plots assess the consistency, robustness, and potential pleiotropy of the instrumental variables used in the analysis.

factor alpha (TNF-α) in perirenal adipose tissue than subjects with normal blood pressure or patients with primary hypertension, and these inflammatory factors can promote an increase in CRP levels in the body [32]. Our study was designed and expanded based on this information to speculate that chronic inflammation in obese individuals leads to elevated CRP levels, thereby mediating the occurrence of benign adrenal tumors. Accordingly, we conducted a Mendelian randomization study to investigate the mediation effect of CRP on benign adrenal tumors through BMI, aiming to explore the underlying mechanisms and provide recommendations for primary prevention of this disease.

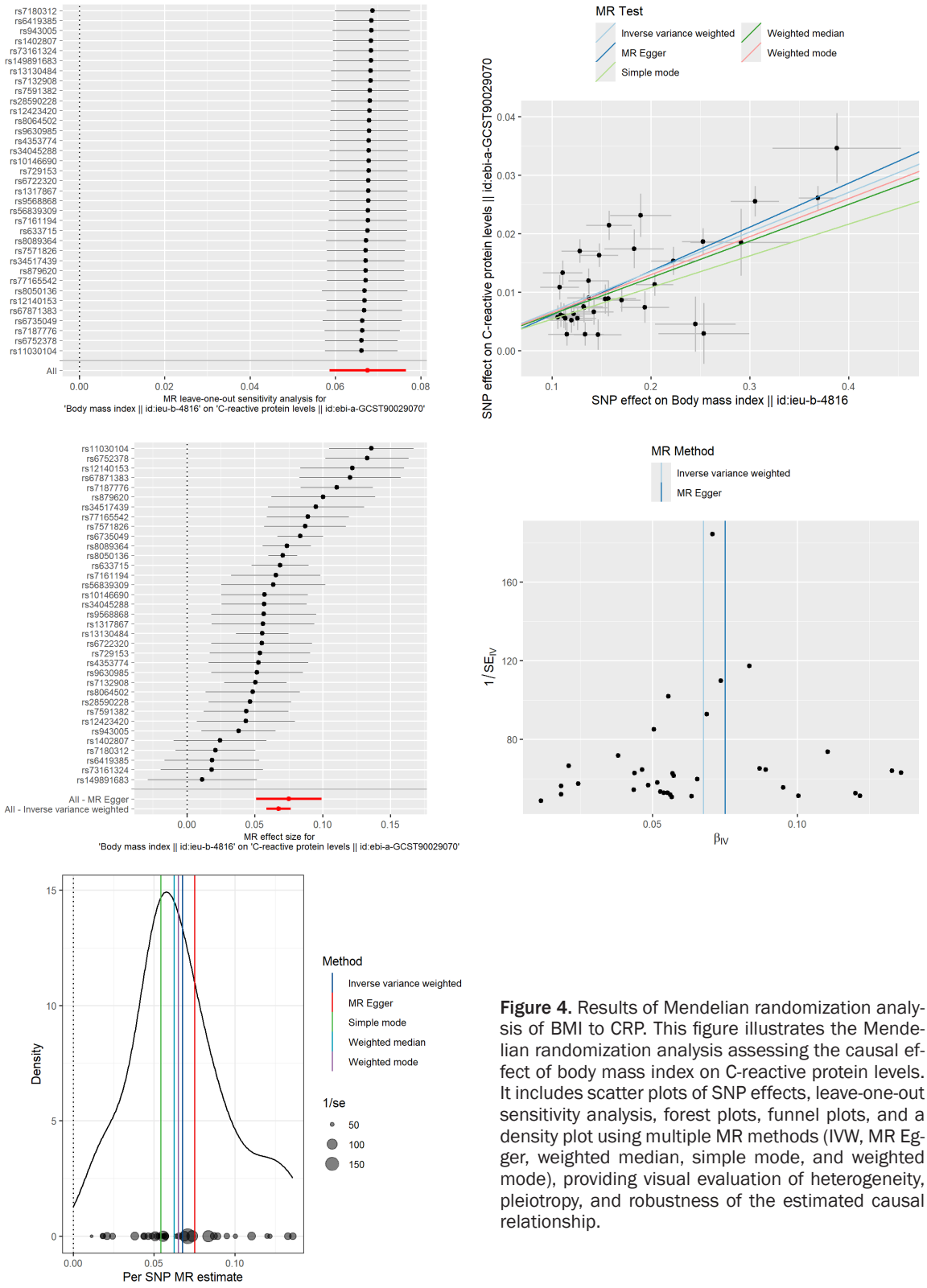

Figure 4. Results of Mendelian randomization analysis of BMI to CRP. This figure illustrates the Mendelian randomization analysis assessing the causal effect of body mass index on C-reactive protein levels. It includes scatter plots of SNP effects, leave-one-out sensitivity analysis, forest plots, funnel plots, and a density plot using multiple MR methods (IVW, MR Egger, weighted median, simple mode, and weighted mode), providing visual evaluation of heterogeneity, pleiotropy, and robustness of the estimated causal relationship.

The diagnosis of adrenal tumors typically relies on CT and/or MRI imaging, as they offer high specificity [33]. However, most benign adrenal tumors are asymptomatic, and thus, clinically, these tumors are mostly incidentally detected through radiological examinations [34, 35].

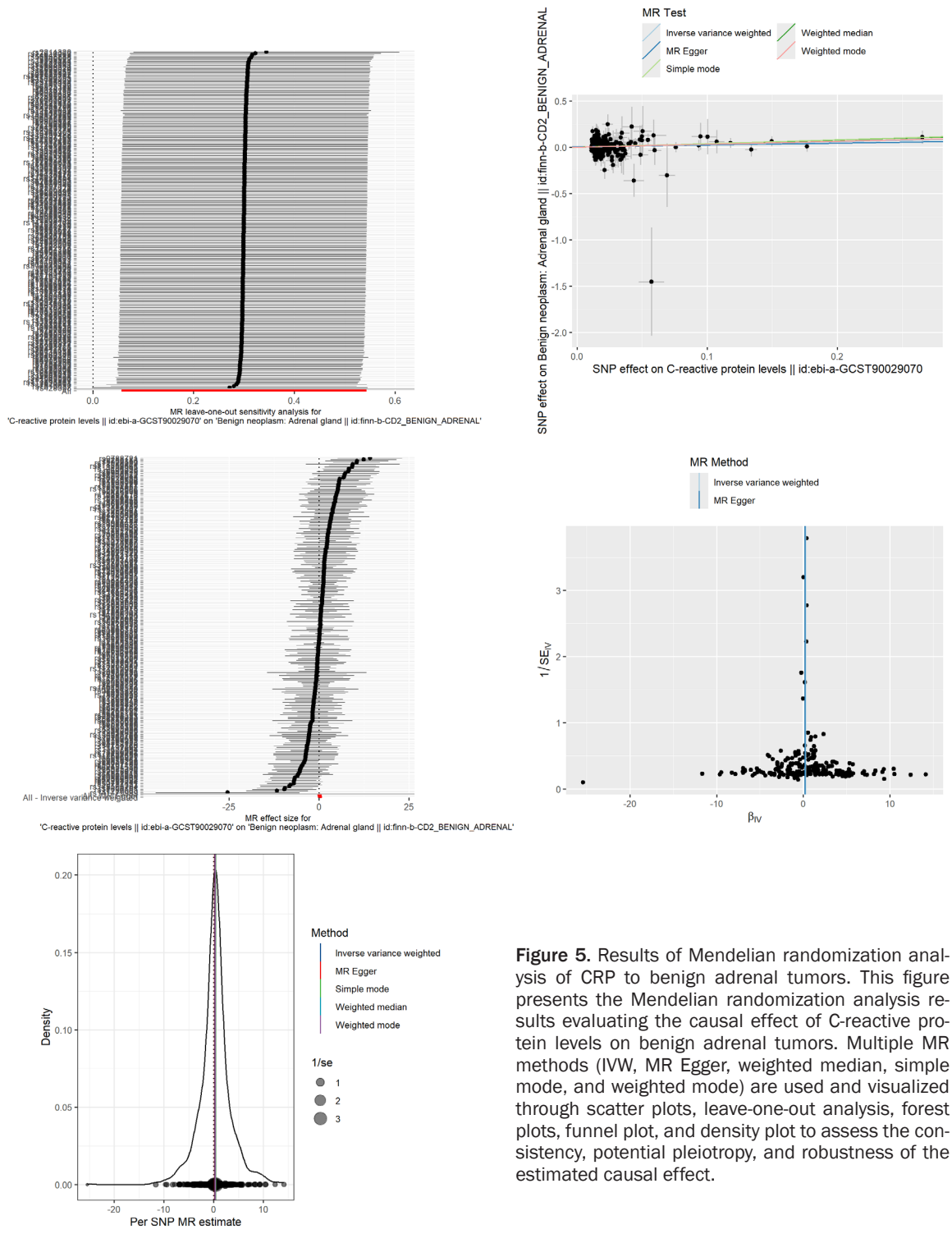

Figure 5. Results of Mendelian randomization analysis of CRP to benign adrenal tumors. This figure presents the Mendelian randomization analysis results evaluating the causal effect of C-reactive protein levels on benign adrenal tumors. Multiple MR methods (IVW, MR Egger, weighted median, simple mode, and weighted mode) are used and visualized through scatter plots, leave-one-out analysis, forest plots, funnel plot, and density plot to assess the consistency, potential pleiotropy, and robustness of the estimated causal effect.

Due to their asymptomatic nature, this disease is often overlooked, and many asymptomatic or mildly symptomatic patients may not actively seek CT scans due to the expense and potential radiation risks associated with the procedure. Hormonal and metabolic testing is also an important diagnostic approach, but it is relatively expensive and may be influenced by medications or other hormones, leading to falsely elevated results [36]. Until corresponding symptoms such as elevated hormone levels or compressive symptoms appear, the dis-

ease may not receive attention. Early identification of these tumors is crucial despite their benign nature, as delayed management can lead to serious health complications. These complications may include hormonal imbalances, severe hypertension, and even metastasis [37, 38]. For example, hormonal imbalances can result in severe hypertension, and larger pheochromocytomas can exert mass effects and invade surrounding tissues [37]. Furthermore, a small subset of benign adrenal tumors may undergo malignant transformation. Therefore, early intervention for benign adrenal tumors is associated with a better prognosis. However, delayed intervention can lead to serious complications, even life-threatening ones.

Our findings indicate that CRP mediates the relationship between BMI and benign adrenal tumors, and it is causally associated with the onset of benign adrenal tumors. Therefore, physicians can enhance their focus on this disease and provide more rational and reliable recommendations by considering both CRP levels and BMI values, thereby reducing the risk of misdiagnosis or underdiagnosis. Based on our research results, theoretically, individuals with obesity can reduce the incidence of benign adrenal tumors by intervening with a healthy lifestyle, which not only decreases CRP levels but also reduces the incidence of benign adrenal tumors. Studies have explicitly shown that lifestyle interventions leading to healthy weight loss significantly reduce CRP levels [39, 40], further indicating a relationship between BMI and CRP levels. Similarly, in terms of diet, pro-inflammatory diets (such as consuming red meat, processed meats, and high-fat diets) lead to elevated CRP levels [41], thus suggesting a potential association with the occurrence of benign adrenal tumors. Given our research results, we speculate that nonsteroidal anti-inflammatory drugs (NSAIDs) may control inflammation, reduce CRP production, and consequently decrease the incidence of benign adrenal tumors. There are already reports indicating that NSAIDs can inhibit IL-6 production and alleviate phenotypes [42]. Mechanistically, by understanding this mechanism, intervening at any stage can reduce the incidence of benign adrenal tumors.

Several observational studies have previously linked obesity with increased adrenal size and altered hormone production, supporting a potential connection between body weight and adrenal tumor development. For instance, Liu et al. [43] found that obesity may persistently increase adrenal gland volume, suggesting a possible mechanism for tumorigenesis through chronic stimulation of adrenal tissue. Our MR findings provide genetic evidence to support this association and further suggest that systemic inflammation, represented by CRP, may mediate this process. Moreover, prior clinical studies have reported that patients with pheochromocytomas often exhibit elevated CRP levels, which tend to decrease after surgical tumor removal, suggesting a link between adrenal tumor activity and systemic inflammation [30]. These observations are consistent with our finding that CRP acts as a partial mediator in the BMI-adrenal tumor relationship. Furthermore, our study has limitations. Obesity, defined as excessive accumulation of body fat beyond healthy levels, can have detrimental effects on health. There are various indicators used to measure obesity, with BMI, WHR (Waist-to-Hip Ratio), and visceral fat mass being among the most common. BMI is the most frequently used measure of obesity. However, in our study, we only used BMI as a measure of obesity, and did not analyze WHR or visceral fat mass.

Conclusion

In clinical practice, we investigated the association between body mass index (BMI), C-reactive protein (CRP), and benign adrenal tumor using Mendelian randomization (MR) methods. We found that BMI may influence the risk of benign adrenal tumor through the mediating effect of CRP. It emphasizes the importance for medical professionals to closely monitor the adrenal health status of obese patients or those with high CRP levels to avoid unnecessary misdiagnosis or underdiagnosis. Moreover, addressing obesity concerns not only involves focusing on physical aspects but also considering the overall inflammatory levels in the body.

This discovery reveals the reasons why obese patients are prone to benign adrenal tumors, contributing to a more comprehensive understanding of the relationship between obesity and benign adrenal glands, as well as their underlying mechanisms. Additionally, it provides new perspectives on intervention strategies from lifestyle modifications, dietary adjustments, to pharmaceutical interventions.

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Disclosure of conflict of interest

None.

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References

[1] Liu F, Chen Y, Xie W, Liu C, Zhu Y, Tian H, Ren Y and Chen T. Obesity might persistently increase adrenal gland volume: a preliminary study. Obes Surg 2020; 30: 3503-3507.

[2] Popoviciu MS, Paduraru L, Nutas RM, Ujoc AM, Yahya G, Metwally K and Cavalu S. Diabetes mellitus secondary to endocrine diseases: an update of diagnostic and treatment particularities. Int J Mol Sci 2023; 24: 12676.

[3] Franco C, Sciatti E, Favero G, Bonomini F, Vizzardi E and Rezzani R. Essential hypertension and oxidative stress: novel future perspectives. Int J Mol Sci 2022; 23: 14489.

[4] Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC and Touyz RM. Oxidative stress and hypertension. Circ Res 2021; 128: 993-1020.

[5] Song M, Liu T, Liu H, Zhang Q, Zhang Q, Wang Y, Ma X, Cao L and Shi H. Association between metabolic syndrome, C-reactive protein, and the risk of primary liver cancer: a large prospective study. BMC Cancer 2022; 22: 853.

[6] Sherlock M, Scarsbrook A, Abbas A, Fraser S, Limumpornpetch P, Dineen R and Stewart PM. Adrenal incidentaloma. Endocr Rev 2020; 41: 775-820.

[7] Ebbehoj A, Li D, Kaur RJ, Zhang C, Singh S, Li T, Atkinson E, Achenbach S, Khosla S, Arlt W, Young WF, Rocca WA and Bancos I. Epidemiology of adrenal tumours in Olmsted County, Minnesota, USA: a population-based cohort study. Lancet Diabetes Endocrinol 2020; 8: 894-902.

[8] Ichijo T, Ueshiba H, Nawata H and Yanase T. A nationwide survey of adrenal incidentalomas in Japan: the first report of clinical and epidemiological features. Endocr J 2020; 67: 141-152.

[9] Lee KY. Cystic pheochromocytoma with hypertensive crisis and classic triad diagnosed using point-of-care ultrasound in the emergency department. J Med Ultrasound 2023; 31: 60-62.

[10] Kizilgul M, Beysel S, Ozcelik O, Kan S, Apaydin M, Caliskan M, Ucan B, Sencar E, Ozdemir S and Cakal E. Pentraxin 3 as a new cardiovascular marker in adrenal adenomas. Endocr Pract 2017; 23: 662-668.

[11] Luan YY and Yao YM. The clinical significance and potential role of C-reactive protein in chronic inflammatory and neurodegenerative diseases. Front Immunol 2018; 9: 1302.

[12] Saltiel AR and Olefsky JM. Inflammatory mechanisms linking obesity and metabolic disease. J Clin Invest 2017; 127: 1-4.

[13] Cucoreanu C, Tigu AB, Nistor M, Moldovan RC, Pralea IE, Iacobescu M, Iuga CA, Szabo R, Dindelegan GC and Ciuce C. Epigenetic and molecular alterations in obesity: linking CRP and DNA methylation to systemic inflammation. Curr Issues Mol Biol 2024; 46: 7430-7446.

[14] Megawati G, Indraswari N, Johansyah AA, Kezia C, Herawati DMD, Gurnida DA and Musfiroh I. Comparison of hs-CRP in adult obesity and central obesity in indonesia based on omega-3 fatty acids intake: indonesian family life survey 5 (IFLS 5) study. Int J Environ Res Public Health 2023; 20: 6734.

[15] Davies NM, Holmes MV and Davey Smith G. Reading Mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 2018; 362: k601.

[16] Silva S, Fatumo S and Nitsch D. Mendelian randomization studies on coronary artery disease: a systematic review and meta-analysis. Syst Rev 2024; 13: 29.

[17] de Leeuw C, Savage J, Bucur IG, Heskes T and Posthuma D. Understanding the assumptions underlying Mendelian randomization. Eur J Hum Genet 2022; 30: 653-660.

[18] Ference BA, Holmes MV and Smith GD. Using Mendelian randomization to improve the design of randomized trials. Cold Spring Harb Perspect Med 2021; 11: a040980.

[19] Sakaue S, Kanai M, Tanigawa Y, Karjalainen J, Kurki M, Koshiba S, Narita A, Konuma T, Yamamoto K, Akiyama M, Ishigaki K, Suzuki A, Suzuki K, Obara W, Yamaji K, Takahashi K, Asai S, Takahashi Y, Suzuki T, Shinozaki N, Yamaguchi H, Minami S, Murayama S, Yoshimori K, Nagayama S, Obata D, Higashiyama M, Masumoto A, Koretsune Y, FinnGen, Ito K, Terao C, Yamauchi T, Komuro I, Kadowaki T, Tamiya G, Yamamoto M, Nakamura Y, Kubo M, Murakami Y, Yamamoto K, Kamatani Y, Palotie A, Rivas MA, Daly MJ, Matsuda K and Okada Y. A cross-population atlas of genetic associations for 220 human phenotypes. Nat Genet 2021; 53: 1415-1424.

[20] Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafo MR, Palmer T, Schooling CM, Wallace C, Zhao Q and Smith GD. Mendelian randomization. Nat Rev Methods Primers 2022; 2: 6.

[21] Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR and Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. Elife 2018; 7: e34408.

[22] Bae SC and Lee YH. Causal association between body mass index and risk of rheumatoid arthritis: a Mendelian randomization study. Eur J Clin Invest 2019; 49: e13076.

[23] Gill D, Karhunen V, Malik R, Dichgans M and Sofat N. Cardiometabolic traits mediating the effect of education on osteoarthritis risk: a Mendelian randomization study. Osteoarthritis Cartilage 2021; 29: 365-371.

[24] Ma MM, Jin CC, Huang XL, Sun L, Zhou H, Wen XJ, Huang XQ, Du JY, Sun HS, Ren ZX, Liu J, Guan YY, Zhao XM and Wang GL. Clcn3 deficiency ameliorates high-fat diet-induced obesity and adipose tissue macrophage inflammation in mice. Acta Pharmacol Sin 2019; 40: 1532-1543.

[25] Ligthart S, Vaez A, Vosa U, Stathopoulou MG, de Vries PS, Prins BP, Van der Most PJ, Tanaka T, Naderi E, Rose LM, Wu Y, Karlsson R, Barbalic M, Lin H, Pool R, Zhu G, Mace A, Sidore C, Trompet S, Mangino M, Sabater-Lleal M, Kemp JP, Abbasi A, Kacprowski T, Verweij N, Smith AV, Huang T, Marzi C, Feitosa MF, Lohman KK, Kleber ME, Milaneschi Y, Mueller C, Huq M, Vlachopoulou E, Lyytikainen LP, Oldmeadow C, Deelen J, Perola M, Zhao JH, Feenstra B, LifeLines Cohort S, Amini M, Group CIW, Lahti J, Schraut KE, Fornage M, Suktitipat B, Chen WM, Li X, Nutile T, Malerba G, Luan J, Bak T, Schork N, Del Greco MF, Thiering E, Mahajan A, Marioni RE, Mihailov E, Eriksson J, Ozel AB, Zhang W, Nethander M, Cheng YC, Aslibekyan S, Ang W, Gandin I, Yengo L, Portas L, Kooperberg C, Hofer E, Rajan KB, Schurmann C, den Hollander W, Ahluwalia TS, Zhao J, Draisma HHM, Ford I, Timpson N, Teumer A, Huang H, Wahl S, Liu Y, Huang J, Uh HW, Geller F, Joshi PK, Yanek LR, Trabetti E, Lehne B, Vozzi D, Verbanck M, Biino G, Saba Y, Meulenbelt I, O'Connell JR, Laakso M, Giulianini F, Magnusson PKE, Ballantyne CM, Hottenga JJ, Montgomery GW, Rivadineira F, Rueedi R, Steri M, Herzig KH, Stott DJ, Menni C, Franberg M, St Pourcain B, Felix SB, Pers TH, Bakker SJL, Kraft P, Peters A, Vaidya D, Delgado G, Smit JH, Grossmann V, Sinisalo J, Seppala I, Williams SR, Holliday EG, Moed M, Langenberg C, Raikkonen K, Ding J, Campbell H, Sale MM, Chen YI, James AL, Ruggiero D, Soranzo N, Hartman CA, Smith EN, Berenson GS, Fuchsberger C, Hernandez D, Tiesler CMT, Giedraitis V, Liewald D, Fischer K, Mellstrom D, Larsson A, Wang Y, Scott WR, Lorentzon M, Beilby J, Ryan KA, Pennell CE, Vuckovic D, Balkau B, Concas MP, Schmidt R, Mendes de Leon CF, Bottinger EP, Kloppenburg M, Paternoster L, Boehnke M, Musk AW, Willemsen G, Evans DM, Madden PAF, Kahonen M, Kutalik Z, Zoledziewska M, Karhunen V, Kritchevsky SB, Sattar N, Lachance G, Clarke R, Harris TB, Raitakari OT, Attia JR, van Heemst D, Kajantie E, Sorice R, Gambaro G, Scott RA, Hicks AA, Ferrucci L, Standl M, Lindgren CM, Starr JM, Karlsson M, Lind L, Li JZ, Chambers JC, Mori TA, de Geus E, Heath AC, Martin NG, Auvinen J, Buckley BM, de Craen AJM, Waldenberger M, Strauch K, Meitinger T, Scott RJ, McEvoy M, Beekman M, Bombieri C, Ridker PM, Mohlke KL, Pedersen NL, Morrison AC, Boomsma DI, Whitfield JB, Strachan DP, Hofman A, Vollenweider P, Cucca F, Jarvelin MR, Jukema JW, Spector TD, Hamsten A, Zeller T, Uitterlinden AG, Nauck M, Gudnason V, Qi L, Grallert H, Borecki IB, Rotter JI, Marz W, Wild PS, Lokki ML, Boyle M, Salomaa V, Melbye M, Eriksson JG, Wilson JF, Penninx B, Becker DM, Worrall BB, Gibson G, Krauss RM, Ciullo M, Zaza G, Wareham NJ, Oldehinkel AJ, Palmer LJ, Murray SS, Pramstaller PP, Bandinelli S, Heinrich J, Ingelsson E, Deary IJ, Magi R, Vandenput L, van der Harst P, Desch KC, Kooner JS, Ohlsson C, Hayward C, Lehtimaki T, Shuldiner AR, Arnett DK, Beilin LJ, Robino A, Froguel P, Pirastu M, Jess T, Koenig W, Loos RJF, Evans DA, Schmidt H, Smith GD, Slagboom PE, Eiriksdottir G, Morris AP, Psaty BM, Tracy RP, Nolte IM, Boerwinkle E, Visvikis-Siest S, Reiner AP, Gross M, Bis JC, Franke L, Franco OH, Benjamin EJ, Chasman DI, Dupuis J, Snieder H, Dehghan A and Alizadeh BZ. Genome analyses of >200,000 individuals identify 58

loci for chronic inflammation and highlight pathways that link inflammation and complex disorders. Am J Hum Genet 2018; 103: 691-706.
[26] Banait T, Wanjari A, Danade V, Banait S and Jain J. Role of High-Sensitivity C-reactive Protein (Hs-CRP) in non-communicable diseases: a review. Cureus 2022; 14: e30225.
[27] Schmidt FM, Weschenfelder J, Sander C, Minkwitz J, Thormann J, Chittka T, Mergl R, Kirkby KC, Faßhauer M, Stumvoll M, Holdt LM, Teupser D, Hegerl U and Himmerich H. Inflammatory cytokines in general and central obesity and modulating effects of physical activity. PLoS One 2015; 10: e0121971.
[28] Ellulu MS, Patimah I, Khaza'ai H, Rahmat A and Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 2017; 13: 851-863.
[29] Toyoda Y, Aiga K, Kometani M and Yoneda T. Acquisition of interleukin-6 production ability over time with pheochromocytoma. JCEM Case Rep 2023; 1: luad106.
[30] Bosanska L, Petrak O, Zelinka T, Mraz M, Widimsky J Jr and Haluzik M. The effect of pheochromocytoma treatment on subclinical inflammation and endocrine function of adipose tissue. Physiol Res 2009; 58: 319-325.
[31] Teno S, Tanabe A, Nomura K and Demura H. Acutely exacerbated hypertension and increased inflammatory signs due to radiation treatment for metastatic pheochromocytoma. Endocr J 1996; 43: 511-516.
[32] Wu C, Zhang H, Zhang J, Xie C, Fan C, Zhang H, Wu P, Wei Q, Tan W, Xu L, Wang L, Xue Y and Guan M. Inflammation and fibrosis in perirenal adipose tissue of patients with aldosterone-producing adenoma. Endocrinology 2018; 159: 227-237.
[33] Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S and Dekkers OM. Management of adrenal incidentalomas: European society of endocrinology clinical practice guideline in collaboration with the European network for the study of adrenal tumors. Eur J Endocrinol 2016; 175: G1-G34.
[34] Araujo-Castro M, García Centeno R, Robles Lázaro C, Parra Ramírez P, Gracia Gimeno P, Rojas-Marcos PM, Fernández-Ladreda MT, Percovich Hualpa JC, Sampedro Núñez M, López-García MC, Lamas C, Álvarez Escolá C, Calatayud Gutiérrez M, Blanco Carrera C, de Miguel Novoa P, Valdés Gallego N, Hanzu F, Marazuela M, Mora Porta M, Mínguez Ojeda C, García Gómez Muriel I, Escobar-Morreale HF and Valderrabano P. Predictive model of pheochromocytoma based on the imaging features of the adrenal tumours. Sci Rep 2022; 12: 2671.
[35] Sundin A, Hindié E, Avram AM, Tabarin A, Pacak K and Taïeb D. A clinical challenge: endocrine and imaging investigations of adrenal masses. J Nucl Med 2021; 62: 26s-33s.
[36] Bokuda K, Yatabe M, Seki Y and Ichihara A. Clinical factors affecting spot urine fractionated metanephrines in patients suspected pheochromocytoma/paraganglioma. Hypertens Res 2020; 43: 543-549.
[37] Chung R, Garratt J, Remer EM, Navin P, Blake MA, Taffel MT, Hackett CE, Sharbidre KG, Tu W, Low G, Bara M, Carney BW, Corwin MT, Campbell MJ, Lee JT, Lee CY, Dueber JC, Shehata MA, Caoili EM, Schieda N and Elsayes KM. Adrenal neoplasms: lessons from adrenal multidisciplinary tumor boards. Radiographics 2023; 43: e220191.
[38] Thomasian NM, Kamel IR and Bai HX. Machine intelligence in non-invasive endocrine cancer diagnostics. Nat Rev Endocrinol 2022; 18: 81-95.
[39] Dvoráková-Lorenzová A, Suchánek P, Havel PJ, Stávek P, Karasová L, Valenta Z, Tintěra J and Poledne R. The decrease in C-reactive protein concentration after diet and physical activity induced weight reduction is associated with changes in plasma lipids, but not interleukin-6 or adiponectin. Metabolism 2006; 55: 359-365.
[40] Larsson A, Hansson LO and Akerfeldt T. Weight reduction is associated with decreased CRP levels. Clin Lab 2013; 59: 1135-1138.
[41] Cayssials V, Buckland G, Crous-Bou M, Bonet C, Weiderpass E, Skie G, Aune D, Heath A, Nøst TH, Masala G, Agnoli C, De Magistris MS, Bueno-de-Mesquita B, Derksen J, Huybrechts I, Ferrari P, Franklin O, Bodén S, Schulze M, Huerta JM, Barricarte A, Sacerdote C, Amiano P, Tumino R, Molina-Montes E, Tjønneland A, Kyrø C, Severi G, Boutron-Ruault MC, Rebours V, Katzke V, Agudo A and Jakszyn P. Inflammatory potential of diet and pancreatic cancer risk in the EPIC study. Eur J Nutr 2022; 61: 2313-2320.
[42] Meijs AC, Schroijen MA, Snel M and Corssmit EPM. Interleukin-6 producing pheochromocytoma/paraganglioma: case series from a tertiary referral centre for pheochromocytomas and paragangliomas. J Endocrinol Invest 2021; 44: 2253-2259.
[43] Liu F, Chen Y, Xie W, Liu C, Zhu Y, Tian H, Ren Y and Chen T. Obesity might persistently increase adrenal gland volume: a preliminary study. Obes Surg 2020; 30: 3503-3507.