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# Evaluating the efficacy of surgical and conservative approaches in mild autonomous cortisol secretion: a meta-analysis

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**Introduction:** The management of Mild Autonomous Cortisol Secretion (MACS) remains a topic of debate among clinicians, with differing opinions on the effectiveness of surgical intervention compared to conservative treatment methods. This meta-analysis provides a comprehensive assessment of available literature to determine the most effective approach for treating this condition.

**Methods:** On December 1, 2023, an exhaustive literature search of English databases Embase, PubMed, the Cochrane Library, Scopus, Web of Science, as well as the Chinese databases China HowNet, Wanfang Database, SinoMed Database, and Weipu Database using the keywords "Mild Autonomous Cortisol Secretion", "Subclinical Cushing's Syndrome", "Subclinical Hypercortisolism", "Mild Cortisol Autonomous Secretion", "Adrenal Incidentaloma", "Surgical Treatment" and "Adrenalectomy". The data were statistically analyzed using STATA version 15.0.

**Results:** In this comprehensive analysis involving 629 patients with MACS, the therapeutic efficacy of adrenalectomy was evident. The meta-analysis results indicate that compared to conservative treatment, surgical intervention more effectively improves obesity indicators in patients: waist circumference (SMD=-0.62, 95% CI: -1.06 to -0.18), BMI (SMD=-0.41, 95% CI: -0.62 to -0.20), enhances glycemic control: fasting blood glucose (SMD=-0.47, 95% CI: -0.68 to -0.26), glycosylated hemoglobin (SMD=-0.66, 95% CI: -0.95 to -0.38), improves lipid metabolism: triglycerides (SMD=-0.45, 95% CI: -0.73 to -0.16), lowers blood pressure: systolic blood pressure (SMD=-1.04, 95% CI: -1.25 to -0.83), diastolic blood pressure (SMD=-0.89, 95% CI: -1.12 to -0.65), and ameliorates hormonal metabolic disorder: 24h urinary free cortisol (SMD=-1.10, 95% CI: -1.33 to -0.87), ACTH (SMD=2.30, 95% CI: 1.63 to 2.97). All these differences are statistically significant.

**Conclusion:** This meta-analysis shows that, compared to conservative treatment, surgical treatment is more effective in improving obesity indicators, glycemic control, lipid metabolism, reducing blood pressure, and ameliorating hormonal metabolic disorders in patients with MACS. These statistically

significant results highlight the importance of considering surgical intervention in the management of patients with MACS.

**Systematic review registration:** <https://www.crd.york.ac.uk/prospero/>, identifier CRD42023492527.

#### KEYWORDS

mild autonomous cortisol secretion, subclinical Cushing's syndrome, subclinical hypercortisolism, mild cortisol autonomous secretion, adrenal incidentaloma, surgical treatment and adrenalectomy mild autonomous cortisol secretion, metabolic disorder, adrenalectomy

## Introduction

Mild Autonomous Cortisol Secretion (MACS) is characterized by an autonomous elevation of cortisol levels within the patient's body, yet it lacks the overt clinical manifestations typically associated with classical Cushing's Syndrome. The diagnostic challenge lies in the mild or indistinct symptoms, necessitating a comprehensive biochemical evaluation for accurate diagnosis (1, 2). The diagnostic cut-offs of MACS based on cortisol values after dexamethasone suppression test (DST) are controversial, The ESE-ENSAT (European Society of Endocrinology-European Network for the Study of Adrenal Tumors) recommended cortisol >1.8 µg/dL (50 nmol/L) after 1 mg-DST rather than 5 µg/dL (138 nmol/L) to define MACS (3–6). With the advancement of imaging techniques, the incidence of adrenal incidentalomas has been progressively increasing. Approximately 5–20% of patients with adrenal incidentalomas exhibit MACS, characterized by subtle alterations in the hypothalamic-pituitary-adrenal axis secretion (1, 2, 7). MACS is associated with osteoporosis, mood alterations, hypertension, abnormalities in glucose and lipid metabolism, increased incidence of cardiovascular diseases, and a higher mortality rate (8–12).

Presently, the comprehension and insights into MACS are in their nascent stages. Research indicates potential therapeutic benefits of adrenalectomy in ameliorating comorbidities associated with MACS. However, the paucity of extensive, randomized controlled trials and the lack of comprehensive long-term postoperative follow-up data hinder the establishment of the unequivocal efficacy of surgical intervention. Consequently, the net clinical advantage of surgical management in MACS continues to be a subject of ongoing medical debate (12–16).

## Methods

On December 1, 2023, an exhaustive literature search of English databases Embase, PubMed, the Cochrane Library, Scopus, Web of Science, as well as the Chinese databases China HowNet, Wanfang

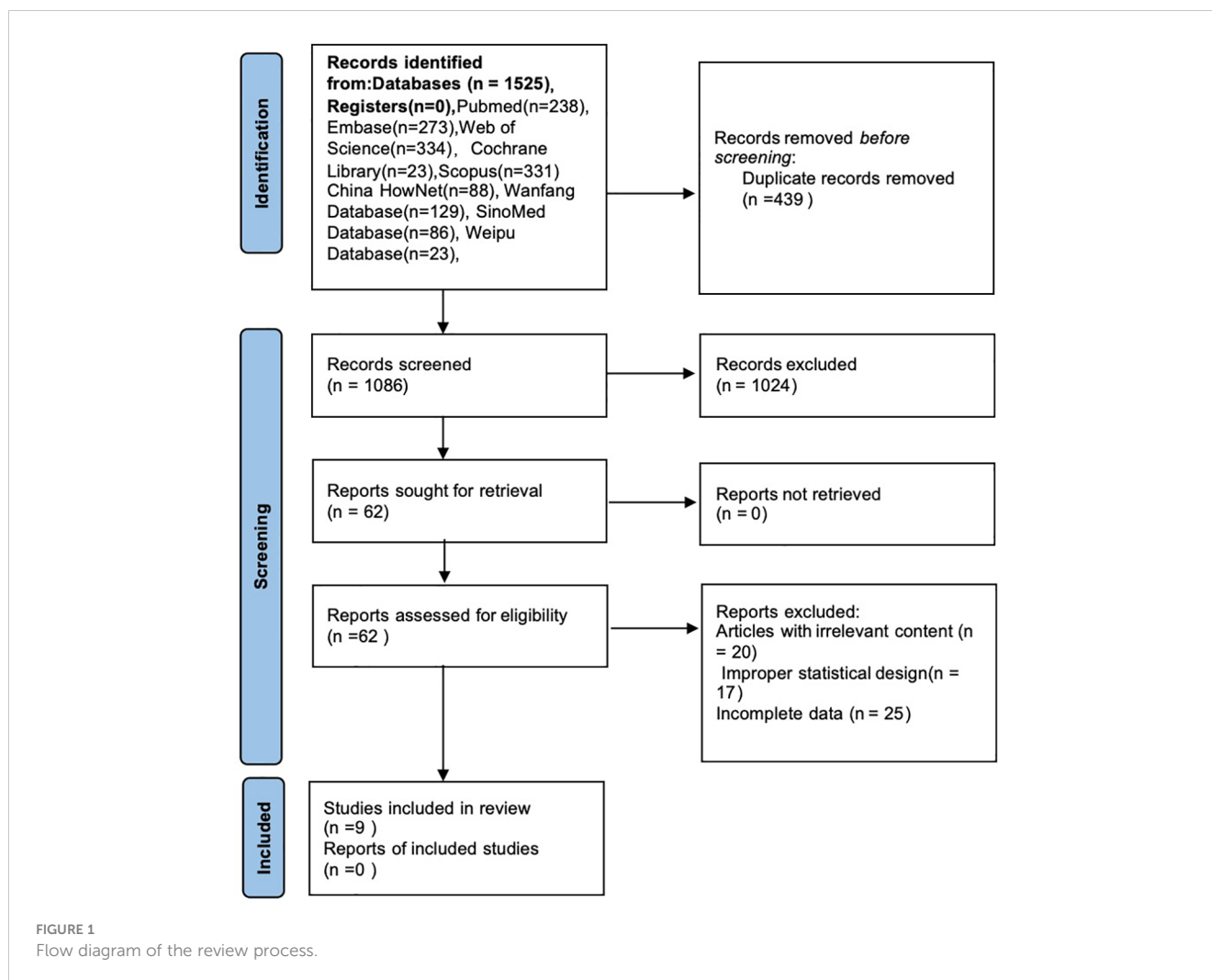
Database, SinoMed Database, and Weipu Database using the keywords “Subclinical Cushing's Syndrome”, “Mild Autonomous Cortisol Secretion”, “Adrenal Incidentaloma”, “Surgical Treatment” and “Adrenalectomy”. A flow-chart of the literature review process is shown in Figure 1. The protocol for this research was registered on the PROSPERO platform (CRD42023492527).

Based on the latest guidelines published by the European Society of Endocrinology (ESE) in 2023, the diagnosis of Mild Autonomous Cortisol Secretion (MACS) primarily relies on the 1mg Dexamethasone Suppression Test (1mg-DST). Specifically, if serum cortisol levels fail to suppress below 1.8 µg/dL (50 nmol/L) after the 1mg dexamethasone suppression test, MACS can be considered (E-ENM) (ESE Home). Additionally, these patients typically do not exhibit the classic clinical features of Cushing's syndrome but may have an increased risk of cardiovascular and metabolic conditions, such as hypertension and type 2 diabetes (Endocrinology.org). The literature included in this study, summarizing the diagnostic criteria for MACS, is compiled in Table 1.

## Study selection and data extraction

The inclusion criteria for this meta-analysis are as follows: 1. Study type: includes randomized controlled trials, cohort studies, and case-control studies. 2. Subjects: patients clearly diagnosed with MACS, at least including (i) no obvious clinical manifestations and signs of hypercortisolism, (ii) patients not suppressed by the 1mg dexamethasone suppression test. 3. Interventions: undergoing adrenalectomy or conservative treatment. 4. The articles should include laboratory test data before and after surgical treatment or before and after conservative treatment (expressed as a continuous numerical variable). Exclusion criteria: 1. Studies not in Chinese or English. 2. Duplicate publications. 3. Reviews, conference proceedings, case reports, and other types of studies. 4. Studies without a clear definition of MACS or without a clear diagnosis.

Two independent reviewers (Ren and Nan) read the literature, selected the studies that met the inclusion and exclusion criteria,



and extracted the study data, including the type of study, date of publication, first author, sample size of each group, intervention measures, follow-up time, and main outcome indicators. In case of disagreement, a third investigator resolved it.

## Quality assessment

The quality of each included study was determined by referring to the Newcastle-Ottawa Scale (NOS).

## Meta-analysis

This meta-analysis was conducted using STATA software, version 15.0. The  $I^2$  test and Q test were employed to assess the heterogeneity among the included studies. When the  $I^2 < 50\%$  and the  $P > 0.1$ , the heterogeneity among the studies is considered to be low, allowing for the use of a fixed-effects model to combine the effect sizes. Otherwise, sensitivity analysis and subgroup analysis can be conducted to explore the sources of heterogeneity, or a random-effects model may be used to combine the effect sizes.

Publication bias was assessed using a funnel plot and Egger's test, with a p-value  $< 0.05$  considered statistically significant.

## Results

### Literature search, basic information, and quality assessments

After the search, a total of 1525 related articles were identified. After removing duplicates, 1086 articles remained. Excluding reviews, case reports, and conference papers left 862 articles. After screening abstracts for relevance, 62 articles remained. Upon full-text reading, articles with irrelevant content, improper statistical design, or those for which the full text could not be obtained were excluded, resulting in 9 (15, 17–24) articles being included in the final analysis. In these 9 articles, conservative treatment refers to oral drug treatment, including oral hypoglycemic drugs, antihypertensive drugs, lipid-lowering drugs and other drugs for hormonal abnormalities comorbidities, not at hypercortisolism itself (e.g. low-dose steroidogenesis inhibitor). The detailed screening process is shown in Figure 1. Table 2 provides

TABLE 1 Characteristics of the studies included in the meta-analysis.

Authors Year Country (ref)	Definition of hypercortisolism	surgical group			non-surgical group		
		Number	Age	follow-up period	Number	Age	follow-up period
Chiodini Iacopo et al. 2009 Italy (11)	MACS defined as Serum cortisol levels after 1 mg dexamethasone suppression test (DST) greater than 3.0 $\mu$ g/dl (83 nmol/liter)	25	54.8 $\pm$ 11.6	29.4 $\pm$ 13.8	16	64.4 $\pm$ 10.1	36.4 $\pm$ 11.6
Zhang W et al. 2007 China (13)	MACS defined as at least one of the three indexes of urine free cortisol, blood cortisol or circadian rhythm disturbance was abnormal at 24h, and the low-dose dexamethasone inhibition test could not inhibit it.	11	49.3 $\pm$ 9.0	25.0 $\pm$ 11.3	37	52.2 $\pm$ 8.9	25.0 $\pm$ 11.3
Liu MS et al. 2020 China (14)	MACS defined as Serum cortisol levels >138 nmol/L at 8:00 AM following suppression with either overnight 1 mg-DST or standard 2 mg-DST.	31	51 $\pm$ 11	11.6 $\pm$ 7.2	11	59 $\pm$ 18	12.0(6.0, 24.0)
Sui H et al. 2019 China (15)	MACS defined as laboratory tests indicating more than two signs of hypothalamic-pituitary-adrenal axis dysfunction, including elevated serum cortisol, increased 24-hour urinary free cortisol, or disrupted diurnal rhythm of cortisol that meets one of the criteria. Additionally, the low-dose dexamethasone suppression test does not show suppression.	18	46.4 $\pm$ 6.5	12	20	47.8 $\pm$ 7.6	12
Wang D et al. 2017 China (16)	MACS defined as at 8:00 AM, measurements of serum adrenocorticotrophic hormone (ACTH), 24-hour urinary-free cortisol (UFC), and the 1 mg overnight dexamethasone suppression test (1 mg-DST) are conducted. At least one abnormal result among these three tests is required for diagnosis, with the result of the 1 mg-DST being the primary basis.	48	52	32	39	53	30
Yilmaz N et al. 2021 Turkey (17)	Patients with a high cortisol level following 1 mg dexamethasone suppression test (DST) and suppressed ACTH level (<10 pg/mL) plus one more positive test result compatible with hypercortisolemia (high cortisol level after two days of 2 mg DST, high 24-hour urinary free cortisol (UFC) level, low dehydroepiandrosteronesulfate (DHEA-S), high late-night salivary cortisol, or midnight serum cortisol level), but no symptoms or signs compatible	57	57(34-75)	21(2-126)	8	65(46-75)	48(10-88)

(Continued)

TABLE 1 Continued

Authors Year Country (ref)	Definition of hypercortisolism	surgical group			non-surgical group		
		Number	Age	follow-up period	Number	Age	follow-up period
	with Cushing's syndrome were considered to have SH.						
Wang D et al. 2018 China (18)	MACS defined as cortisol levels greater than 1.8 $\mu$ g/dL after 1-mg DST.	48	51.8 $\pm$ 10.2	32.5 $\pm$ 10.6	39	53.2 $\pm$ 12.1	30.1 $\pm$ 13.1
Iacobone Maurizio et al. 2012 Italy (19)	MACS defined as morning serum cortisol levels greater than 5 $\mu$ g/dL after the administration of 1 mg of dexamethasone in the evening the day before; morning ACTH levels less than 10 pg/mL, and daily urinary-free cortisol (UFC) greater than 76 $\mu$ g/day.	20	57(36-78)	54 $\pm$ 34	15	58(39-75)	56 $\pm$ 37
Salcuni Antonio Stefano et al. 2016 Italy (20)	Diagnosed SH by the absence of signs and/or symptoms of cortisol excess (i.e. striae rubrae, moon facies, buffalo hump, and skin atrophy) and by the presence (in at least two out of three different estimations) of cortisol levels after 1 mg overnight dexamethasone suppression (1 mg-DST) >5.0 $\mu$ g/dl (138 nmol/l) or in the presence of greater than or equal to two out of the following alterations: 1 mg-DsT >3.0 $\mu$ g/d (83 nmol/l), adrenocorticotropic hormone (ACTH) levels <10 pg/ml (2.2 pmol/l), 24h urinary free cortisol (UFC) levels >70 $\mu$ g/24 h (193 nmol/24 h).	32	65.4 $\pm$ 7.05	39.9 $\pm$ 20.9	23	61.3 $\pm$ 8.7	27.7 $\pm$ 11.1

MACS, Mild autonomous cortisol secretion; SH, Subclinical hypercortisolism; DST, Dexamethasone suppression test.

information on the included studies, all of which were scored using the NOS (Newcastle-Ottawa Scale) with scores of 6 or above, as detailed in Table 2. The characteristics of the studies included in the meta-analysis, including the diagnostic criteria for MACS, are summarized in Table 1.

## Changes in obesity indicators

Two studies were included that reported changes in waist circumference between surgical patients and those receiving conservative treatment. Heterogeneity testing resulted in  $I^2 = 0.0\%$ ,  $p = 0.517$ , indicating very little heterogeneity in the selection of studies for this research. Therefore, a fixed-effects model was used to combine effect sizes. The results showed that, compared to the conservative treatment group, the change in waist circumference was more significant in the surgical group (SMD = -0.62, 95% CI: -1.06 to -0.18;  $p < 0.05$ ) (Figure 2).

Five studies were included that assessed changes in BMI between surgical patients and those receiving conservative

treatment. After testing for heterogeneity,  $I^2 = 34.1\%$ ,  $p = 0.194$ , indicating very little heterogeneity in the selection of studies for this research. Therefore, a fixed-effects model was employed to combine effect sizes. The results showed a more significant reduction in BMI in the surgical group (SMD = -0.41, 95% CI: -0.62 to -0.20;  $p < 0.05$ ). (Figure 3). The funnel plot (Supplementary Figure S1) and Egger's test ( $p = 0.624$ ) showed no publication bias.

## Glucose metabolism

Seven studies were included that reported on the changes in fasting blood glucose between surgical patients and those receiving conservative treatment, with  $I^2 = 43.6\%$  and  $p = 0.101$ , indicating significant heterogeneity among the included studies. Therefore, a random effects model was chosen to pool the effect sizes. The results showed that, compared to conservative treatment, surgery was more effective in reducing patients' fasting blood glucose (MD = -0.47, 95% CI: -0.68 to -0.26;  $p < 0.05$ ) (Figure 4). The funnel plot

TABLE 2 Basic information and quality evaluation of previous research.

Author	Year	Type	NOS			
			Selection	Comparability	Outcome	Scores
Zhang	2007	Case-control study	☆☆	☆☆	☆☆☆	7☆
Liu	2020	Case-control study	☆☆	☆☆	☆☆☆	7☆
Sui	2019	Cohort study	☆☆	☆☆	☆☆	6☆
Wang	2017	Case-control study	☆☆☆	☆☆	☆☆☆	8☆
Yilmaz	2021	Case-control study	☆☆☆	☆☆	☆☆☆	8☆
Wang	2018	Case-control study	☆☆☆	☆☆	☆☆☆	8☆
Salcuni	2016	Case-control study	☆☆☆	☆☆	☆☆☆	8☆
Iacobone	2012	Cohort study	☆☆☆	☆☆	☆☆	7☆
Chiodini	2009	Case-control study	☆☆☆	☆☆	☆☆☆	8☆

☆ indicates a score of one point in the evaluation.

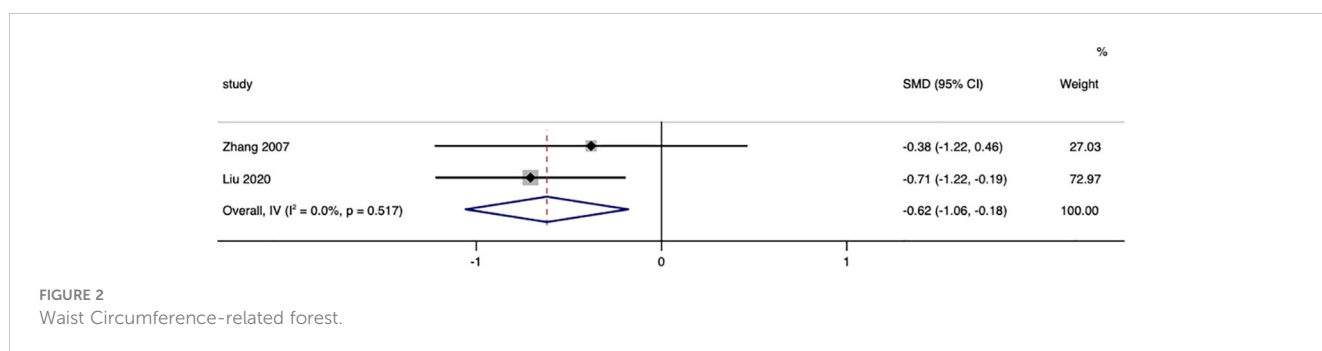


FIGURE 2 Waist Circumference-related forest.

(Supplementary Figure S2) and Egger’s test ( $p < 0.05$ ) indicated the presence of publication bias.

Three studies were included that reported on the changes in glycated hemoglobin (HbA1c) between surgical patients and those receiving conservative treatment, with  $I=0.0\%$  and  $p=0.713$ , indicating very low heterogeneity among the studies. A fixed-effect model was used to pool the effect sizes. The results showed that, compared to conservative treatment, surgery was more effective in reducing patients’ HbA1c (SMD= -0.66, 95% CI: -0.95 to -0.38;  $p < 0.05$ ) (Figure 5).

### Lipid metabolism

A total of six studies compared the changes in triglycerides between surgical patients and those receiving conservative treatment, with an  $I=85.0\%$  and  $p=0.000$ , indicating a high level of heterogeneity in the literature selection for this study. Upon investigating the sources of heterogeneity and excluding the studies by N. Yilmaz and Liu, a re-evaluation of heterogeneity showed an  $I=0.0\%$  and  $p=0.490$ . Therefore, a random effects model was used to pool the effect sizes. The results demonstrated that surgery could

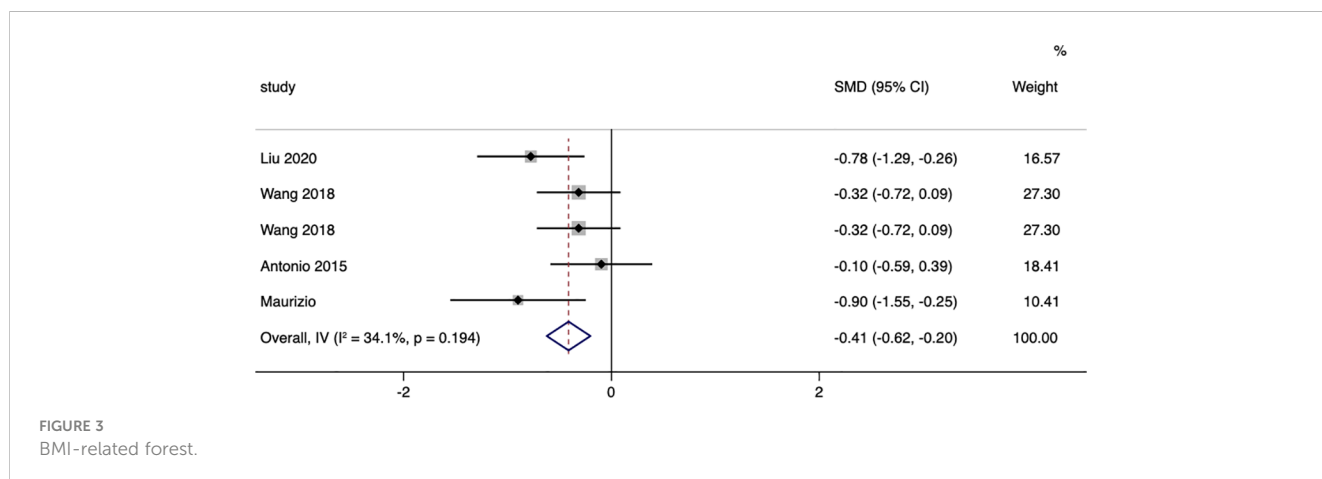


FIGURE 3 BMI-related forest.

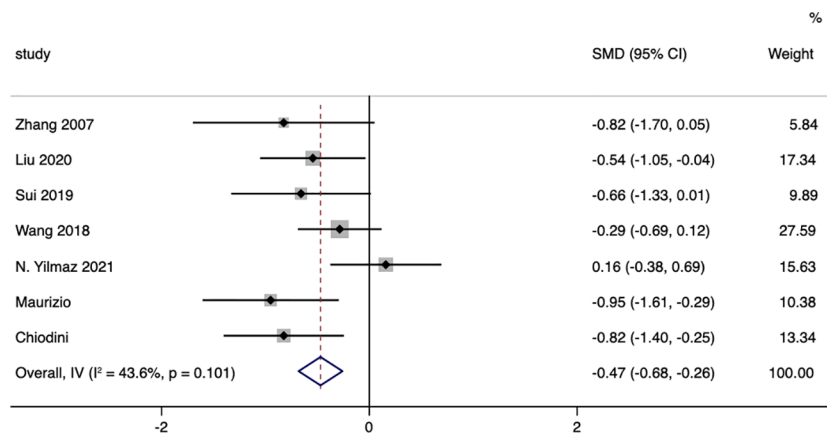


FIGURE 4  
Fasting Blood Glucose-related forest.

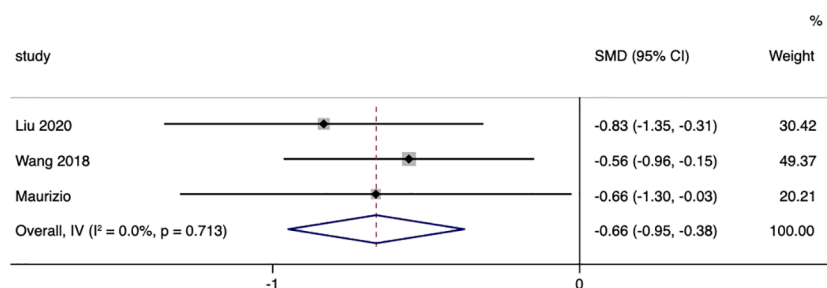


FIGURE 5  
Glycated Hemoglobin (HbA1c)-related forest.

reduce triglycerides in patients, with a standardized mean difference (SMD=-0.45, 95% CI: -0.73 to -0.16; p<0.05) (Figure 6). The funnel plot (Supplementary Figure S3) and Egger’s test (p=0.260) showed no publication bias.

A total of five studies compared the changes in LDL (low-density lipoprotein) between surgical patients and those receiving conservative treatment, with an I=0.0% and p=0.349, indicating

very low heterogeneity in the selection of literature for this study. Therefore, a fixed-effect model was used to pool the effect sizes. The results showed that, compared to the conservative group, surgery did not significantly reduce LDL in patients, with a standardized mean difference (SMD=0.17, 95% CI: -0.09 to 0.42; p=0.203) (Figure 7). The funnel plot (Supplementary Figure S4) and Egger’s test (p=0.221) showed no publication bias.

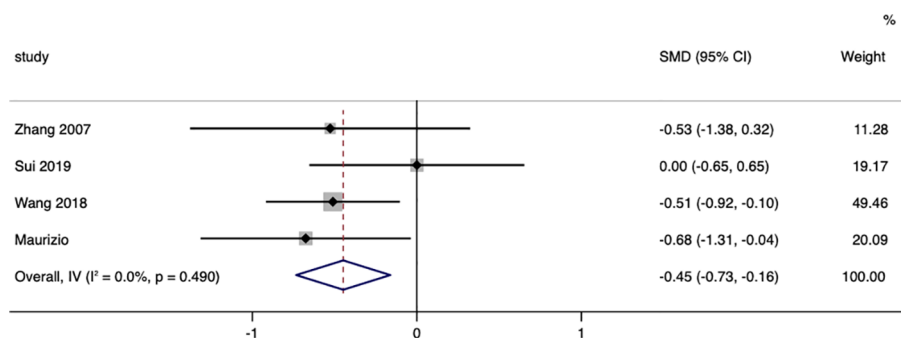


FIGURE 6  
Triglycerides-related forest.



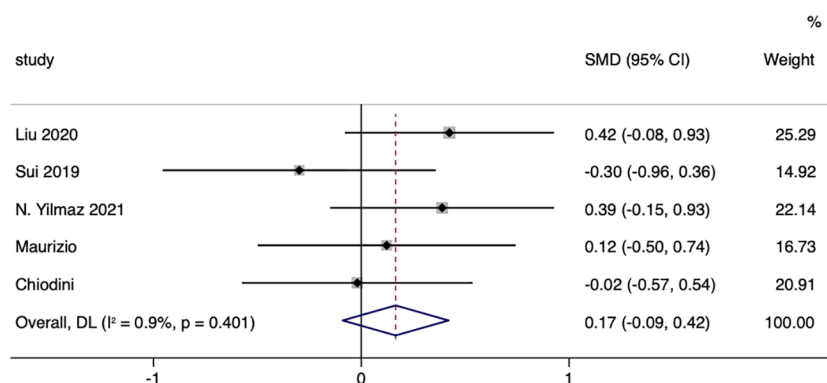


FIGURE 7  
LDL-related fourrest.

### In terms of blood pressure

In terms of systolic blood pressure, a total of seven studies compared the changes in systolic blood pressure between surgical patients and those receiving conservative treatment, with an  $I^2=0.0\%$  and  $p=0.874$ , indicating very low heterogeneity in the selection of literature for this study. Therefore, a fixed-effect model was used to pool the effect sizes. The results showed that, compared to the conservative treatment group, surgery was more effective in reducing patients' systolic blood pressure (SMD= -1.04, 95% CI: -1.25 to -0.83;  $p<0.05$ ) (Figure 8). The funnel plot (Supplementary Figure S5) and Egger's test ( $p=0.293$ ) showed no publication bias.

A total of six studies compared the changes in diastolic blood pressure between patients in the surgical group and those receiving conservative treatment, with an  $I^2=0.0\%$  and  $p=0.805$ , indicating very low heterogeneity in the selection of literature for this study. Therefore, a fixed-effect model was used to pool the effect sizes. The results showed that, compared to the conservative treatment group, surgery was more effective in reducing patients' diastolic blood pressure, with a standardized mean difference (SMD= -0.89, 95%

CI: -1.12 to -0.65;  $p<0.05$ ) (Figure 9). The funnel plot (Supplementary Figure S6) and Egger's test ( $p<0.05$ ) indicated the presence of publication bias.

### Hormone levels

A total of five studies compared the changes in 24-hour urinary free cortisol levels between patients in the surgical group and those receiving conservative treatment, with an  $I^2=0.0\%$  and  $p=0.441$ , indicating very low heterogeneity in the selection of literature for this study. Therefore, a fixed-effect model was used to pool the effect sizes. The results showed that, compared to the conservative treatment group, surgery resulted in a more significant decrease in patients' 24-hour urinary free cortisol levels, with a standardized mean difference (SMD= -1.10, 95% CI: -1.33 to -0.87;  $p<0.05$ ) (Figure 10). The funnel plot (Supplementary Figure S7) and Egger's test ( $p=0.851$ ) showed no publication bias.

A total of six studies compared the changes in ACTH (Adrenocorticotropic Hormone) levels between patients in the

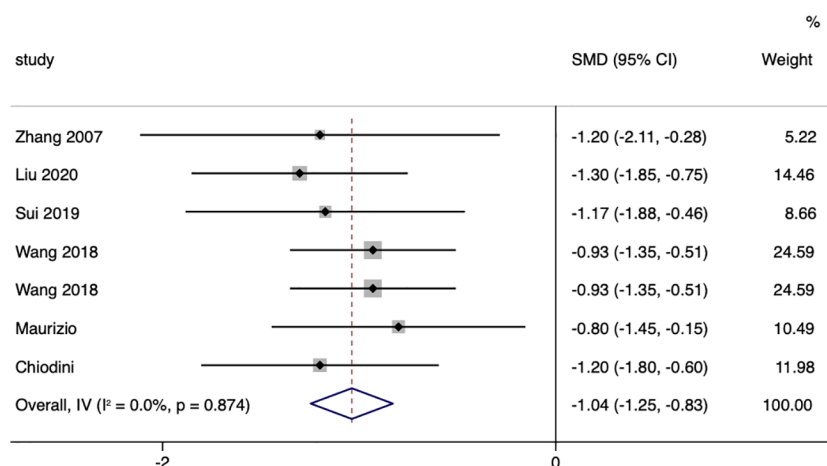


FIGURE 8  
Systolic Blood Pressure-related forest.



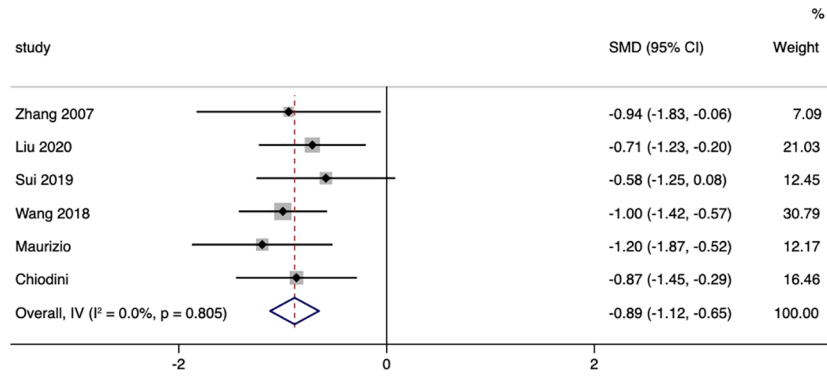


FIGURE 9  
Diastolic Blood Pressure-related forest.

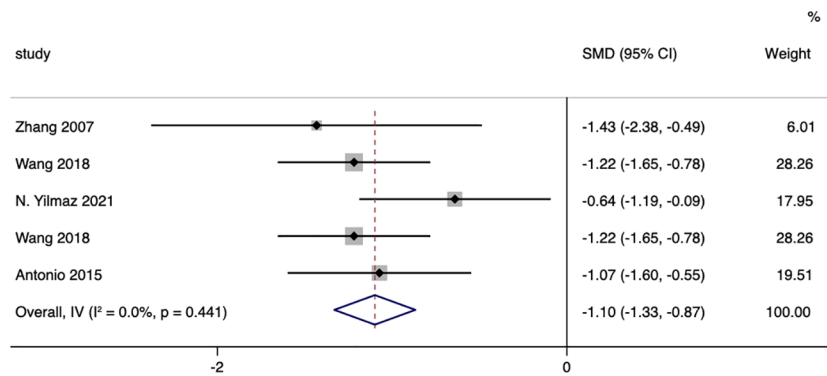
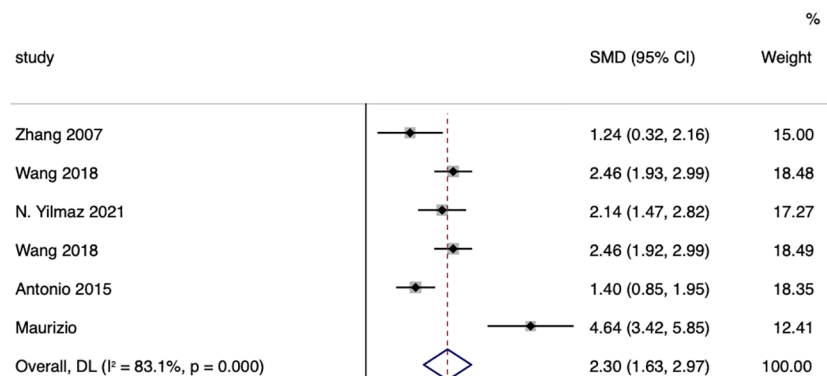


FIGURE 10  
24-hour Urinary Free Cortisol-related forest.

surgical group and those receiving conservative treatment, with an  $I^2=83.1\%$  and  $p=0.00$ , indicating a high level of heterogeneity in the selection of literature for this study. Therefore, a random effects model was used to pool the effect sizes. The results showed that,

compared to the conservative treatment group, surgery was able to increase patients' ACTH levels ( $MD= 2.30, 95\% CI: 1.63$  to  $2.97; p<0.05$ ) (Figure 11). The funnel plot (Supplementary Figure S8) and Egger's test ( $p< 0.05$ ) indicated the presence of publication bias.



NOTE: Weights are from random-effects model

FIGURE 11  
ACTH-related forest.

## Discussion

With the maturation and widespread use of ultrasound and CT imaging technologies, the incidence of adrenal tumors has gradually increased. Among adrenal incidentalomas, approximately 5% to 20% are functional adenomas that produce glucocorticoids (1, 2, 25). Mild Autonomous Cortisol Secretion (MACS) refers to a condition in which the adrenal cortex, often in the context of an adrenal adenoma or other adrenal lesions, autonomously secretes mildly elevated levels of cortisol without stimulation from adrenocorticotropic hormone (ACTH). This condition typically lacks the overt clinical symptoms of Cushing's syndrome. Studies have shown that patients with MACS are more likely to develop metabolic diseases such as hypertension, type 2 diabetes, obesity, and dyslipidemia compared to patients without cortisol abnormalities. These conditions significantly increase the risk of cardiovascular events and death (11, 26–32).

A 15-year retrospective study analyzing data from 118 patients with adrenal incidentalomas found a significant correlation between MACS and cardiovascular events and mortality. Compared to patients without hormone abnormalities, those with MACS had higher rates of cardiovascular events and mortality (33). The possible pathophysiological mechanisms are: Cortisol increases blood pressure by activating mineralocorticoid receptors, leading to sodium retention and increased blood volume. It also induces insulin resistance, promoting the development of type 2 diabetes, which further elevates cardiovascular risk. Moreover, cortisol dysregulation results in lipid metabolism abnormalities, increasing levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides, which enhance atherosclerotic processes.

Chronic low-grade inflammation is another critical pathophysiological mechanism. Elevated cortisol levels in MACS induce a systemic inflammatory response, marked by increased inflammatory markers such as C-reactive protein and interleukin-6. This inflammation damages endothelial function and promotes arterial stiffness, further exacerbating cardiovascular risk. Additionally, chronic inflammation contributes to endothelial dysfunction, which impairs vascular health and increases the likelihood of cardiovascular events (34, 35).

However, the absence of overt Cushing's syndrome symptoms makes the condition easy to overlook or misdiagnose, leading to potential under-treatment. Under-treatment can result from the failure to recognize the cardiovascular risks associated with MACS. Without appropriate intervention, these patients remain at elevated risk for adverse cardiovascular outcomes. Our statistical analysis results show that, compared to conservative treatment, surgery can improve glucose and lipid metabolism in patients with MACS, reduce blood pressure and weight, and improve hormone levels, which is similar to the conclusions of some previous studies (29, 36–42). In the management of subclinical Cushing's syndrome, adrenalectomy as a treatment option has been shown in multiple studies to have significant benefits for patients. Specifically, surgical treatment, compared to conservative management, demonstrates higher efficacy in improving or curing metabolic diseases associated with MACS, such as hypertension, glucose metabolism disorders, and

obesity. A systematic review revealed that, in the group of patients who underwent adrenalectomy, 72%, 46%, and 39% of patients achieved cure or significant improvement in blood pressure control, glucose metabolism, and weight management, respectively (43). Studies have suggested that cardiovascular risk factors worsened in patients with MACS in the medically managed group (14, 15, 23, 44). Among the MACS population, patients with osteoporosis have a higher incidence of fractures (45–47). Due to the limitations of the included literature, we were unable to analyze the impact of surgery on osteoporosis in such patients.

Minimally invasive adrenalectomy has been proven to be a safe and effective treatment strategy, demonstrating good clinical outcomes associated with a low risk of complications, even in patients with MACS (48). These research findings highlight the importance and clinical benefits of adopting adrenalectomy for treating MACS under specific circumstances. However, unnecessary adrenalectomy in the treatment of mild autonomous cortisol secretion (MACS) can lead to adverse outcomes due to the ambiguous criteria for surgical intervention. Studies indicate that adverse outcomes post-adrenalectomy include postoperative adrenal insufficiency, persistent hypertension, and the failure to improve certain components of the metabolic syndrome. One study highlighted that a subset of MACS patients undergoing adrenalectomy continued to experience complications such as hypertension and diabetes. Additionally, surgical complications such as bleeding, infection, and postoperative adrenal crisis must be considered. The long-term effects of surgical treatment and lifestyle interventions still require further research and validation (49–51).

Conservative treatment (including pharmacotherapy and lifestyle modifications) offers an alternative treatment approach for patients who are at a higher risk from surgery or who refuse surgical interventions. This method also has the advantages of being less invasive and having a smaller impact on the patient's daily life, despite its lesser effectiveness in controlling symptoms and reducing complications compared to surgical treatment (52).

Inconsistencies in the diagnostic criteria for patients with MACS lead to heterogeneity in the study populations, which may affect the evaluation of surgical and conservative treatment outcomes. Furthermore, there is still a lack of high-quality, large-scale randomized controlled studies to confirm the best management strategy for patients with MACS. Both surgical and conservative treatments have their advantages and limitations. Choosing the best treatment approach requires a comprehensive consideration of the patient's specific conditions, preferences, potential risks, and expected treatment outcomes. Future research should focus on comparing the long-term effects of surgical versus conservative treatment and developing personalized treatment strategies to improve the treatment outcomes and quality of life for patients with MACS.

## Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The data comes from published studies. Requests to access these datasets should be directed to [709069446@qq.com](mailto:709069446@qq.com).

## Author contributions

XR: Writing – original draft. MN: Writing – original draft, Methodology. XZ: Writing – review & editing, Supervision.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fendo.2024.1399311/full#supplementary-material>

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