BMC Endocrine Disorders

SYSTEMATIC REVIEW

Open Access

Metabolic complications and clinical outcomes of non-functioning adrenal incidentalomas: a systematic review and meta-analysis

Xiaolan Li[1†], Huiyu Lan[1†], Xinying Lin[1], Huibin Huang[1], Junping Wen[1], Gang Chen[1] and Wei Lin[1*]

Abstract

Background Increased detection of non-functioning adrenal incidentalomas (NFAI) due to widespread abdominal imaging may underestimate associated metabolic risks. To examine NFAI's impact on metabolic comorbidities and evaluate outcomes in surgical and non-surgical management, including changes in NFAI characteristics during follow-up.

Methods Meta-analysis of studies from PubMed, Embase, Cochrane Library, and Web of Science (January 2000 to May 2024). Studies focusing on patients with serum cortisol levels ≤ 50 nmol/L after 1 mg dexamethasone suppression test (DST). Prevalence of hypertension, diabetes, obesity, and lipid disorders before and after follow-up. Tumor growth (> 10 mm increase) and functional changes (1 mg DST retest) were assessed.

Results Eighteen studies met inclusion criteria ($n = 2,059$). In the non-surgical group, diabetes (RR: 1.33, 95% CI: 1.07–1.65) and lipid disorders (RR: 1.22, 95% CI: 1.07–1.38) increased significantly, while hypertension (RR: 1.07, 95% CI: 0.99–1.16) and obesity (RR: 1.05, 95% CI: 0.91–1.21) showed no significant change. Surgical intervention significantly improved hypertension (RR: 0.67, 95% CI: 0.52–0.86). During mean follow-up of 46.1 months, 4% (95% CI: 2%- 8%) of NFAI enlarged > 10 mm, while 8% (95% CI: 5%- 14%) became functional during 45.1 months of follow-up.

Conclusions In patients with NFAI, subtle hormone secretion may exist despite current diagnostic criteria suggesting non-functionality. Such tumors show significant associations with metabolic disorders, particularly diabetes mellitus and dyslipidemia. Future research should focus on developing more sensitive diagnostic methods and establishing evidence-based surgical intervention criteria through prospective studies.

Keywords Adrenal incidentaloma (AI), Non-functioning adrenal incidentaloma, Metabolic comorbidities, Surgical management, Non-surgical management

Introduction

Over the last two decades, the prevalence of adrenal incidentalomas, defined as adrenal tumors larger than 1 cm, has surged tenfold, largely due to the widespread use of computed tomography (CT) scans [1, 2]. Studies suggest a prevalence of 3% in individuals over 50, escalating to 10% in those over 80, indicating an age-related increase [3]. While functional adrenal incidentalomas

†Xiaolan Li and Huiyu Lan have contributed equally to this work.

*Correspondence:
Wei Lin
caolalin0929@163.com
[1] Department of Endocrinology, Fujian Provincial Hospital, Shengli Clinical Medical College of Fujian Medical University, Fuzhou University Affiliated Provincial Hospital, No. 134 Dongjie Street, Gulou District, Fuzhou, Fujian, China

are known to correlate with metabolic syndrome, recent Euro 2023 guidelines delineate mild autonomous cortisol secretion (MACS) as cortisol levels surpassing 50 nmol/L following a 1 mg overnight dexamethasone test (DST), recommending surgical evaluation for MACS patients presenting with comorbidities [3]. In contrast, non-functioning adrenal incidentaloma (NFAI) cases, where cortisol levels are below 50 nmol/L, and which are generally not advised for surgical intervention [3].

Emerging studies, however, signal a considerably higher risk of type 2 diabetes and cardiovascular diseases in NFAI patients relative to those with normative adrenal functionality, indicating a potentially overlooked metabolic disease risk associated with NFAI [4, 5]. Some research further suggests that surgical treatment of NFAI can significantly ameliorate outcomes related to hypertension [6–8]. Motivated by these findings, we perform a systematic review and meta-analysis aimed at discerning the impact of NFAI on metabolic conditions, including hypertension, diabetes, obesity, and lipid metabolism disorders over time.

Furthermore, the long-term clinical trajectory of NFAI, particularly concerning potential changes in tumor size and functionality during natural follow-up, remains inadequately explored. In this study, we categorized the included studies into surgical and non-surgical management groups to evaluate the progression of these features in NFAI. Through this comprehensive analysis, we aim to elucidate the metabolic implications of NFAI, and the outcomes associated with different management approaches. Our goal is to inform future research directions and contribute to the development of more personalized clinical management strategies for NFAI patients, taking into account the complex relationship between these tumors and metabolic health.

Method

Literature search

Our meta-analysis followed a pre-established protocol based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA registration number CRD42023483006) [9] guidelines, which were established on January 16, 2017.

Two reviewers (X.L. and H.L.) independently conducted a comprehensive search of PubMed, Embase, Cochrane Library, and Web of Science from January 1, 2000, to May 1, 2023. Additionally, we examined the reference lists of relevant articles to identify any potentially missed studies during our electronic search. To ensure a thorough search, we used the broad term"adrenal incidentaloma"to capture all relevant articles. The detailed search strategies are provided in the supplementary material (Appendix 1). An updated search was conducted in May 2024.

Literature selection

Our predefined selection criteria are as follows:

1) Included Population: ①Studies were eligible if they involved individuals with adrenal tumors larger than 1 cm detected on imaging performed for reasons unrelated to the hypothalamic-pituitary-adrenal axis, while known malignant tumors were excluded. ②Hormone examinations were performed to rule out overt adrenal hormone excess conditions such as Cushing's syndrome, pheochromocytoma, or primary hyperaldosteronism. The initial screening measured levels of cortisol, plasma aldosterone, plasma renin activity, epinephrine, and other catecholamines, and when abnormalities were detected, confirmatory tests were performed—specifically, an overnight dexamethasone suppression test or a 48-h, 2 mg/day dexamethasone suppression test (LDDST: dexamethasone 0.5 mg orally every 6 h for 2 days) for suspected autonomous cortisol secretion, a saline loading test or captopril test for suspected primary hyperaldosteronism, and iodine- 123 metaiodobenzylguanidine scintigraphy for suspected pheochromocytoma [10]. ③ Patients were classified as having non-functioning adrenal incidentalomas if their serum cortisol levels were below 50 nmol/L (1.8 μg/dL) after a dexamethasone suppression test, following current clinical guidelines [3].
2) Studies included in the meta-analysis reported on subjects divided into either a surgical group or a non-surgical group. The surgical group consisted of subjects who underwent adrenal tumor resection. Surgical methods varied and included laparoscopic adrenalectomy, with some studies specifying partial or total adrenalectomy. The non-surgical group consisted of subjects who were followed conservatively for a minimum period of 12 months. Not all studies included both surgical and non-surgical groups; some studies focused solely on one approach.
3) Required Outcomes: We included studies that reported changes in tumor diameter and hormone production in the non-surgical group during follow-up. Additionally, studies had to report at least one of the following metabolic outcomes: diabetes, hypertension, lipid disorders, and obesity. For each metabolic parameter, we analyzed the changes by comparing pre- and post-follow-up data within individual studies using their respective diagnostic crite-

ria. Studies were included if they provided data for these comparisons.

Our predefined exclusion criteria were as follows:

1) Non-English Articles: Studies published in languages other than English were excluded.
2) Non-relevance to NFAI: Articles that did not pertain to non-functioning adrenal incidentalomas were excluded.
3) Lack of Required Data: Articles with incomplete data or data that did not meet the specified requirements were not considered.

The selection process involved two independent reviewers, X.L. and H.L., who applied these criteria. Any discrepancies were resolved through discussion and consensus with the third author, W.L.

Data extraction and comprehensive analysis

In this section, we outline our data extraction process and the parameters we collected from each eligible study to meet our research needs. These parameters include the last name of the first author, country of the study, year of publication, study design, the number of eligible patients, their ages, duration of follow-up, body mass index (BMI), and male-to-female ratio.

We followed patients who were nonfunctional at baseline, regardless of any functional changes during follow-up. The criterion for assessing comorbidity was the number of patients diagnosed with the specific disease. Hypertension, diabetes, obesity, and lipid disorders were evaluated before and after the follow-up, based on the original definition criteria presented in the respective papers. Relative risk (RR) was the prevalence ratio before and after follow-up.

Changes in tumor size during follow-up were determined by counting the number of individuals whose tumor diameter increased by more than 10 mm [4]. Changes in hormone production were assessed based on the results of the retest of the 1 mg DST test. If serum cortisol levels after the 1 mg DST were equal to or greater than 50 nmol/L, we considered it a functional change. The proportion represents the percentage of individuals who experienced changes after follow-up.

During data collection, we recorded continuous variables as either the mean or median, and categorical variables as the total number and the number of positive cases. Our data extraction followed specific rules to ensure consistency and accuracy.

We conducted our data analysis using R software (version 4.2.2, https://www.R-project.org) and the R package Meta. Outcome data served as the central study parameter for our meta-analysis. We reported pooled mean differences (MDs) with 95% confidence intervals (CIs). All statistical tests were two-sided, and statistical significance was considered for *p*-values less than 0.05 ($P < 0.05$).

To assess heterogeneity between studies, we used the I^2 statistic. The I^2 index quantifies the proportion of total variation attributable to between-study heterogeneity, calculated as $[(Q–df) \div Q] \times 100\%$, where Q represents the Cochran's Q statistic and df represents degrees of freedom (number of studies minus one) [11]. I^2 values range from 0 to 100%, with higher values indicating greater heterogeneity. We interpreted I^2 values below 50% as low heterogeneity and values above 50% as substantial heterogeneity.

Based on the heterogeneity assessment, we employed a fixed-effect model when heterogeneity was low ($I^2 < 50\%$) and a random-effects model when heterogeneity was substantial ($I^2 > 50\%$) [12–14]. To evaluate the impact of model selection on our results, we calculated effect estimates using both fixed-effect and random-effects models for all outcomes. For outcomes with substantial heterogeneity ($I^2 > 50\%$), we also conducted sensitivity analyses using a one-by-one exclusion method. We performed subgroup analyses for outcomes with more than 6 included studies, stratifying by age, follow-up duration, and BMI. Publication bias was assessed using funnel plots for outcomes with eight or more included studies, following established methodological guidelines. This minimum threshold of eight studies was selected to ensure reliable interpretation of funnel plot asymmetry [15].

Quality assessment

The quality assessment process carried out by two independent reviewers (X.L. and H.L.) for each included study. We adapted the Newcastle–Ottawa scale [16] to evaluate the quality of studies included in the meta-analysis based on the PICO (Patient, Intervention, Comparison, Outcome) framework [10]. Details are shown in the supplementary material (Appendix 2).

Result

Characteristics of included studies

Our meta-analysis included 18 studies, comprising a total cohort of 2,059 patients diagnosed with NFAI. The initial literature search covered January 2000 to August 21, 2023, identifying 17 studies. An updated search extending to May 2024 yielded one additional eligible study, resulting in our final inclusion of 18 studies.. The study selection process is illustrated in Fig. 1. A comprehensive summary of the study characteristics is presented in Table 1. Among the 12 studies that reported BMI data,

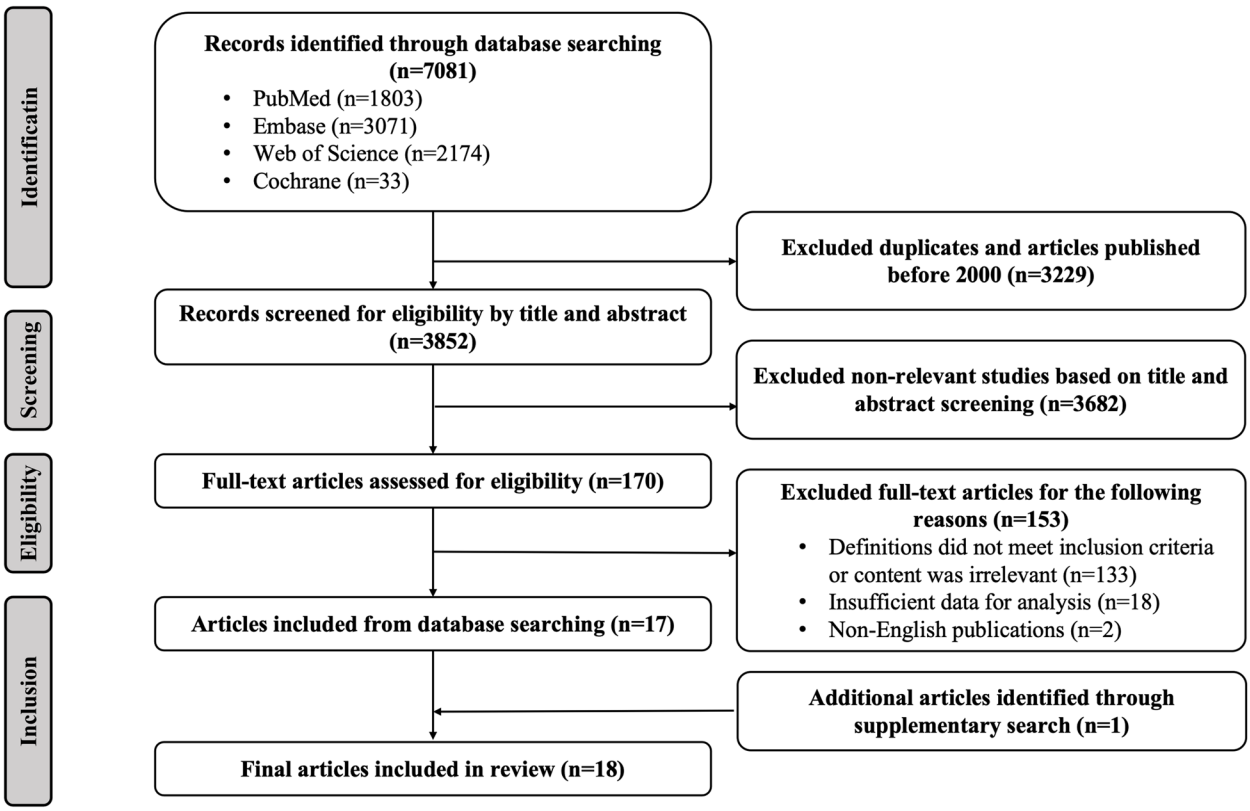

Fig. 1 Study flow diagram. Flow chart outlining the number of records identified, included, and excluded and the reasons for the exclusion

values ranged from 24.5 to 30.7 kg/m^2, with an overall average of 27.76 kg/m^2, suggesting a tendency toward overweight status in the NFAI population.

The included studies were categorized into two groups, noting that two studies spanned both categories:

(1) Non-surgical group: This comprised 16 studies (11 retrospective and 5 prospective), including 1,916 NFAI patients. The mean age across these studies ranged from 50.3 to 66.4 years, with follow-up periods varying between 18 and 126.1 months.
(2) Surgical group: This included 4 studies (3 retrospective and 1 prospective), involving 214 patients who underwent adrenal tumor resection. The average patient age in these studies ranged from 50.5 to 53.2 years. Surgical methods varied among the studies: ① One study did not specify the exact procedure. ② One study primarily used laparoscopic partial adrenalectomy. ③ Two studies mentioned either total or partial adrenalectomy. The reasons for surgical intervention varied among the studies but generally included: ① Tumor characteristics (size > 3.5–4 cm, suspicious imaging features, or growth). ②Patient-specific factors (metabolic issues, concurrent procedures, hypertension, or preference).

Metabolic comorbidity changes in NFAI patients by treatment group during follow-up

Hypertension

In the non-surgical group, which included 720 NFAI patients from six studies [17, 18, 23, 24, 28, 33], the baseline prevalence of hypertension was 58.3%. Over an average follow-up period of 55.78 months, 30 out of 300 initially hypertension-free patients developed hypertension, representing a 4.2% (30/720) increase in prevalence. The relative risk (RR) of developing hypertension post-follow-up was 1.07 (95% CI: 0.99–1.16), as shown in Fig. 2A. Although this RR does not reach statistical significance, it suggests a trend towards an increased prevalence of hypertension among NFAI patients.

The surgical group, analyzed from four articles [7, 24, 31, 32], included 214 NFAI patients, with 196 presenting hypertensions at baseline. Post-surgery, 70 patients'hypertension resolved, a 32.7% reduction. The prevalence ratio (0.67, 95% CI: 0.52–0.86) shows a

Table 1 Demographic, clinical, and methodological characteristics of included studies on non-functioning adrenal incidentalomas

First author	Country	Design	Year	N	M/F	Follow-up (months)	Age at initial diagnosis (years)	BMI (kg/m^2)	Post-DST cortisol (nmol/l)	Surgical Method	Reasons for Surgery
Remde H et al. 2023 [6]	German	Retrospective	2023	123	54/69	105.6*	57.0*	N/A	35.7*	N/A	N/A
Podbregar A et al. 2021 [17]	Slovenia	Prospective	2021	67	20/47	126.1*	57.9*	27.42*	28*	N/A	N/A
Araujo-Castro M et al. 2021 [18]	Spain	Retrospective	2021	305	136/169	41.3*	61.5	29.3	32.95	N/A	N/A
Falcetta P et al. 2020 [19]	Italy	Retrospective	2020	209	77/132	31.4*	57.3	28.8	30.21*	N/A	N/A
Ruiz A et al. 2019 [20]	Spain	Retrospective	2019	70	40/30	48*	66.4	N/A	N/A[a]	N/A	N/A
Hong AR et al. 2017 [21]	Korea	Retrospective	2017	193	N/A	34.8*	57.2	N/A	N/A[a]	N/A	N/A
Patrova J et al. 2017 [22]	Sweden	Retrospective	2017	204	82/122	62.4	60.5	28.7	32.3	N/A	N/A
Papanastasiou L et al. 2016 [23]	Greece	Prospective	2016	51	15/36	66.48	56.5	28.3	30.35	N/A	N/A
Xu TY et al. 2014 [7]	China	Retrospective	2014	109	50/59	24	53.6	24.5	33.23	N/A	N/A
Vasilev V et al. 2014 [24]	Bulgaria	Retrospective	2014	94	N/A	18*	53.2	28.7	N/A[a]	N/A	N/A
Dalmazi GD et al. 2014 [25]	Italy	Retrospective	2014	129	52/77	90	61.3	28.5	31.2	N/A	N/A
Ng VW et al. 2010 [26]	Chinese Hong Kong	Retrospective	2010	61	N/A	30.2*	57.4	N/A	N/A[a]	N/A	N/A
Yener S et al. 2010 [27]	Turkey	Prospective	2010	120	N/A	24*	56.3	N/A	36.52	N/A	N/A
Giordano R et al. 2010 [28]	Italy	Prospective	2010	102	41/61	36*	61.9	26.8	43.94	N/A	N/A
Vassilatou E et al. 2009 [29]	Greece	Prospective	2009	57	N/A	60*	58	30.7	21.7	N/A	N/A
Vilar L et al. 2008 [30]	Brazil	Retrospective	2008	22	N/A	24.8	50.3	N/A	N/A[a]	N/A	N/A
Xia WJ et al. 2016 [31]	China	Retrospective	2016	90	38/52	59.2	50.86	26.49	29.93	Total or partial adrenalectomy (transabdominal or retroperitoneoscopic)	Surgery for high blood pressure
Xu TY et al. 2014 [7]	China	Retrospective	2014	77	32/45	24	52.2	24.9	34.33	Total or partial adrenalectomy	Tumor diameter ≥ 4 cm, growth on imaging, concurrent laparoscopic procedures, patient preference because of metabolic issues
Vasilev V et al. 2014 [24]	Bulgaria	Retrospective	2014	38	N/A	18	53.2	N/A	N/A[a]	Adrenalectomy (specific method not mentioned)	Tumor size > 40 mm, suspected malignancy, hormone hypersecretion, tumor growth during follow-up
Bernini G et al. 2003 [32]	Italy	Prospective	2003	9	1/8	12	50.5	N/A	N/A[a]	Laparoscopic adrenalectomy	Tumor diameter > 3.5 cm, malignant imaging features, tumor growth

Most of the above data are averages, using the median for large dispersion*

Most were tested with 1 mg overnight dexamethasone, while a few articles performed 2-day 2 mg DST involving the administration of 0.5 mg oral dexamethasone given every 6 h for 48 h [7, 19, 23, 27, 28, 30]

N Number of NFAI patients, *M/F* Male/Female, *DST* Dexamethasone suppression test, *N/A* Not Applicable

All patients included were tested for low-dose dexamethasone, but average values were not provided in some articles[a]

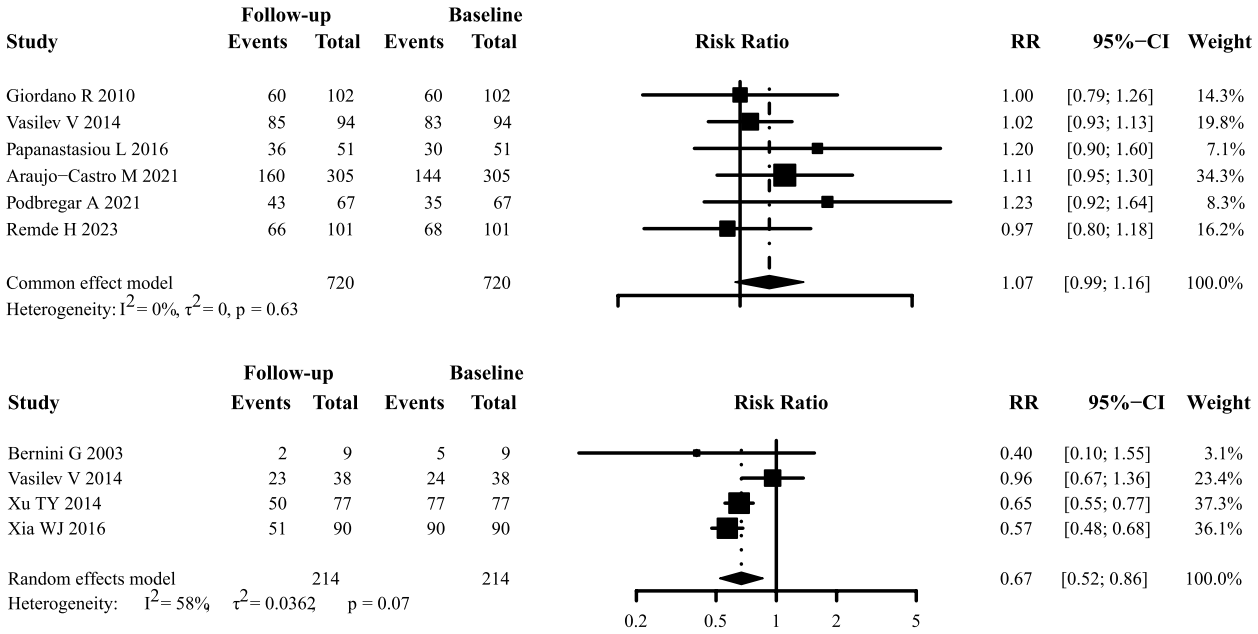

Fig. 2 Hypertension outcomes in non-surgical vs. surgical management of NFAI. Depicts the prevalence and development of hypertension in patients with NFAI under non-surgical management. B: Shows the change in hypertension prevalence among NFAI patients following surgical intervention

significant decrease in hypertension, despite study heterogeneity (Fig. 2B).

Diabetes mellitus, obesity, and dyslipidemia

Our analysis encompassed multiple metabolic comorbidities in NFAI patients:

Diabetes mellitus: Five studies [17, 18, 23, 24, 33] focusing on diabetes, involving a total of 618 NFAI patients. Throughout the follow-up period, averaging 59.5 months, we observed a 6.3% increase in diabetes prevalence. This change represents a significant rise, with a relative risk of 1.33 (95% CI: 1.07–1.65), as highlighted in Fig. 3A.

Obesity: Data from three studies [18, 24, 33] included 508 patients in the non-surgical group. Throughout a mean follow-up of 53 months, obesity prevalence increased by 2.2%. The relative risk was 1.05 (95% CI: 0.91–1.21), suggesting a non-significant trend towards higher obesity rates in NFAI patients (Fig. 3B).

Dyslipidemia: Four studies [18, 23, 24, 33] were analyzed, with an average follow-up duration of 54.2 months. The prevalence of dyslipidemia increased notably by 8.8%, yielding a relative risk of 1.22 (95% CI: 1.07–1.38). This significant increase is shown in Fig. 3C.

Changes of adrenal tumor characteristics in NFAI patients under non-surgical management

In the non-surgical group of NFAI patients, changes in tumor size and hormonal function were monitored over time. Five studies [17, 18, 26, 30, 34] examined significant diameter increases (> 10 mm) while seventeen studies [6, 7, 17–30] evaluated functional changes in adrenal incidentalomas.

As shown in Fig. 4, 4% (95% CI: 2%– 8%) of 556 patients experienced a tumor diameter increase exceeding 10 mm over an average follow-up of 46.1 months. Additionally, 8% (95% CI: 5%– 14%) of 1,845 patients transitioned from non-functioning to functioning adrenal tumors over an average follow-up of 45.13 months.

Sensitivity analysis

We evaluated the impact of model selection by comparing results from both fixed-effect and random-effects models for all outcomes. The statistical significance and

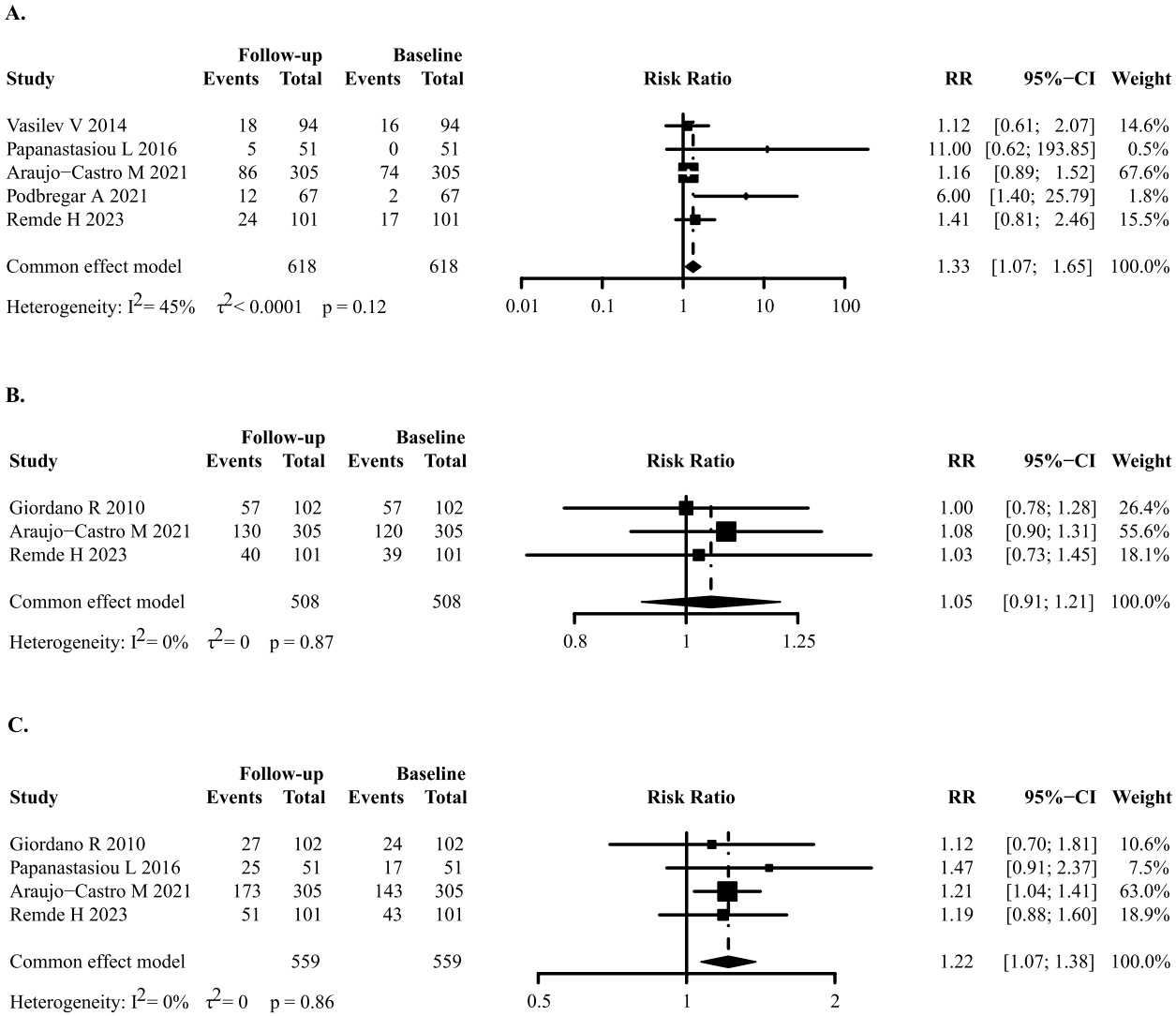

Fig. 3 Metabolic comorbidity outcomes in non-surgical management of NFAI. **A** Illustrates the impact of non-surgical management on diabetes prevalence among NFAI patients. **B** Depicts the prevalence of obesity in NFAI patients under non-surgical management. **C** Outlines the prevalence of lipid metabolism disorders in the non-surgical NFAI cohort

effect directions remained consistent across both models, confirming that model selection did not alter our main conclusions (Supplementary Table S1). For outcomes with substantial heterogeneity (I^2 > 50%), we performed sensitivity analyses using a one-by-one exclusion method to identify potential sources of heterogeneity (Supplementary Figure S1).

Subgroup analyses for functional changes revealed significant associations with BMI and follow-up duration, but not with age (Supplementary Table S2). In BMI-stratified analysis, functional change rates were 1% (95% CI: 0.00–0.05) in the 24–27 kg/m^2 group, 13% (95% CI: 0.11–0.15) in the 27–30 kg/m^2 group, and 14% (95% CI: 0.06–0.26) in the > 30 kg/m^2 group, with heterogeneity observed in the 27–30 kg/m^2 subgroup (I^2 = 89%). Follow-up duration analysis showed functional changes increasing from 4% (95% CI: 0.02–0.07) at 18–30 months to 22% (95% CI: 0.13–0.34) at > 90 months, with intermediate values of 18%, 15%, and 21% at 30–42, 42–66, and 66–90 months, respectively. Age stratification showed no consistent pattern, with rates of 2%, 22%, 9%, and 0% across progressive age groups (Supplementary Table S2).

Publication bias assessment using funnel plots was conducted for outcomes with eight or more included studies. For specific complications in surgical and non-surgical groups, the number of available studies was fewer than eight. Funnel plot analysis was performed for functional changes as shown in Supplementary Figure S2.

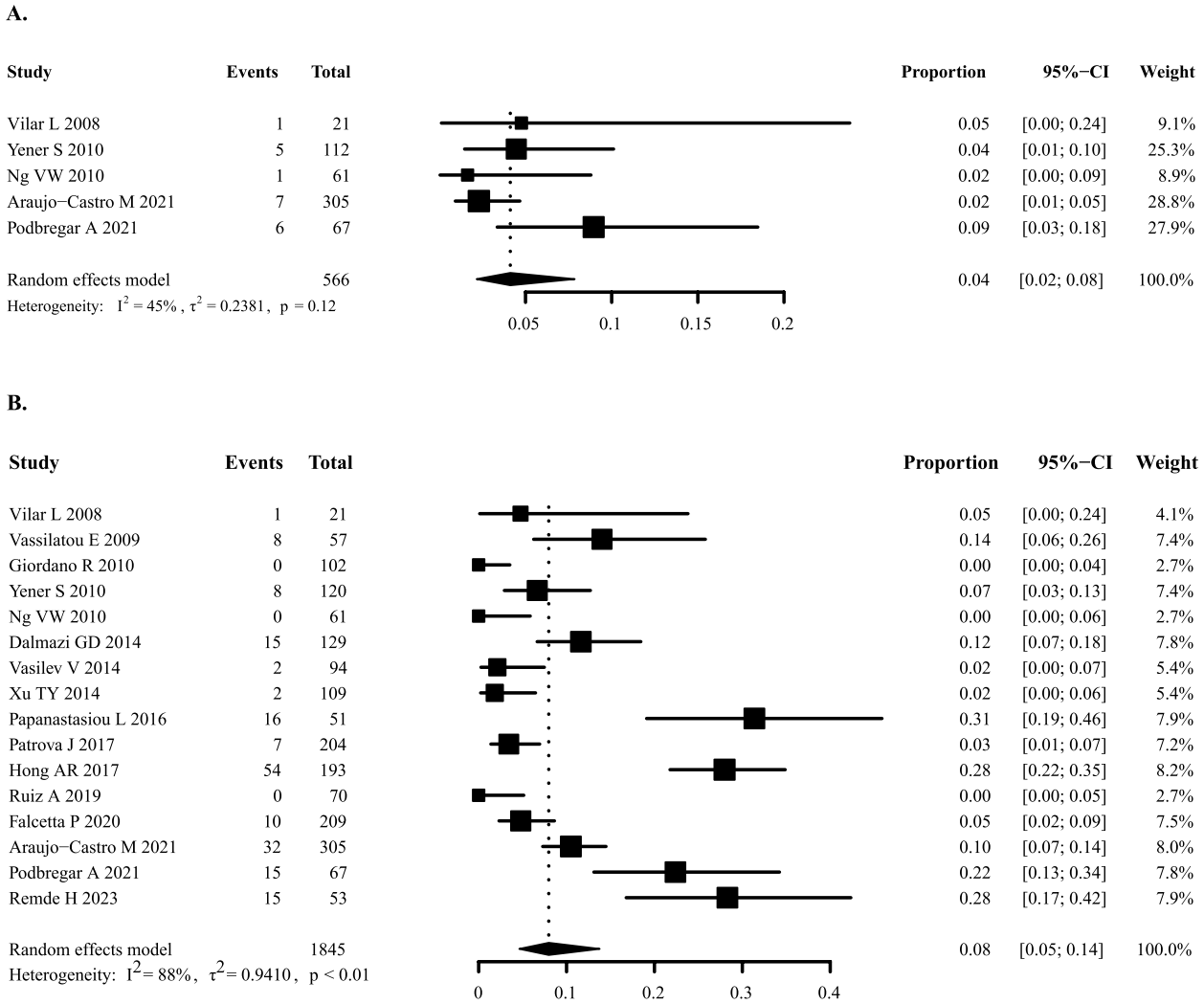

Fig. 4 Tumor characteristics and hormonal function changes in non-surgical NFAI management. **A** Tumor size evolution in non-surgically managed NFAI patients. Depicts the percentage of NFAI patients who experienced a significant increase (> 10 mm) in tumor diameter during the follow-up period in the non-surgical group. **B** Hormonal function alterations in non-surgically managed NFAI patients. Illustrates the proportion of patients within the non-surgical cohort who exhibited changes in hormonal function, transitioning towards a functional adrenal incidentaloma status during follow-up

Discussion

Our systematic review and meta-analysis reveal significant metabolic implications associated with NFAI. Notably, we observed a marked increase in the prevalence of diabetes mellitus and dyslipidemia among patients managed non-surgically over the follow-up period. This finding aligns with previous research indicating a twofold increase in diabetes risk for NFAI patients compared to individuals without adrenal tumors [35]. Recent evidence has clarified previously inconsistent findings, highlighting increased insulin resistance [36] and a greater prevalence of type 2 diabetes [37] in this population.

Several factors may contribute to these observations. Firstly, the age range of our study population (50.3 to 66.4 years for non-surgical and 50.5 to 53.2 years for surgical groups) represents a demographic with an inherently higher risk for metabolic disorders. Secondly, current limitations in diagnosing functional adrenal tumors may lead to misclassification, with patients exhibiting subtle hormonal secretion potentially being overlooked. This diagnostic challenge could contribute to the observed increase in metabolic syndrome frequency, suggesting a more complex etiological role of NFAI in metabolic disturbances than previously thought.

To better understand these diagnostic challenges and metabolic implications, research by Androulakis et al. [36] and others [38] delves deeper into the relationship between NFAI and metabolic health, suggesting increased insulin resistance and endothelial dysfunction could be attributable to subtle cortisol excess. These findings illuminate the complex interplay between hormonal activity and metabolic health, emphasizing the importance of recognizing and managing subclinical cortisol excess in NFAI. Our meta-analysis supports this concept, revealing that approximately 4% of patients experienced significant tumor diameter enlargement during follow-up, while about 8% showed functional changes (Fig. 4). This suggests that NFAI may not be entirely nonfunctional and could evolve into tumors with secretory capabilities, influencing the development of metabolic complications. The observed trend of increasing functional changes and metabolic complications with longer follow-up periods suggests a possible time-dependent relationship that may warrant clinical consideration. These observations raise the question of whether NFAIs might potentially serve as indicators of metabolic vulnerability in some patients, which could support the value of periodic metabolic screening even when initial hormonal evaluations are normal.

Our findings also reveal a mean BMI exceeding 24 kg/m2 among patients, indicative of the broader trend of obesity within the NFAI cohort. Subgroup analysis demonstrated that both BMI and follow-up duration were significantly associated with the incidence of functional changes. The larger the BMI subgroup (from 24–27 kg/m^2 to > 30 kg/m^2), the greater the proportion of nonfunctional tumors developing functional changes (from 1 to 14%). Similarly, longer follow-up durations showed progressively increasing rates of functional changes (from 4% at 18–30 months to 22% at > 90 months). This observation underlines the critical role of central obesity in the pathogenesis of metabolic syndrome [39], resonating with the literature on adipose tissue's endocrine function and its exacerbation of metabolic issues [40].

Our analysis suggests the potential benefits of surgical intervention, particularly in improving hypertension outcomes in NFAI patients. While these findings are preliminary, the comparison between surgical and non-surgical outcomes requires careful interpretation. The surgical cohort was selected based on specific criteria including large tumor size, concerning imaging features, tumor growth, or severe hypertension. This selection bias, combined with the smaller surgical cohort size, suggests the need for cautious interpretation of the metabolic outcomes. Future studies, particularly randomized controlled trials, would help further validate these initial findings and better define the role of surgery in managing metabolic complications of NFAI.

Our sensitivity analyses revealed important sources of heterogeneity. For tumor diameter changes, the heterogeneity was primarily attributed to two studies [17, 18]; removal of these studies significantly reduced heterogeneity. However, for functional changes, heterogeneity persisted even after sensitivity analyses, likely due to substantial differences in sample sizes across studies. The funnel plot analysis suggested publication bias, potentially reflecting a follow-up bias where patients with larger adenomas or higher cortisol levels were more likely to continue follow-up care, particularly those showing potential for functional changes.

These findings collectively highlight several key aspects of NFAI's metabolic impact: (1) the significant association with diabetes mellitus and dyslipidemia, particularly in patients managed non-surgically; (2) the potential role of subtle cortisol excess in metabolic complications, supported by our observation that 8% of patients developed functional changes during follow-up; and (3) the possible benefits of surgical intervention in selected cases, especially for hypertension management. Given these complex interactions, comprehensive long-term monitoring strategies are essential, with particular attention to hormonal changes and metabolic parameters. Future research should prioritize well-designed prospective studies and randomized controlled trials to address specific gaps, including the standardization of hormonal assessments, the comparison of surgical versus non-surgical outcomes in matched populations, and the evaluation of long-term metabolic implications in different patient subgroups.

Our study has several important limitations that warrant careful consideration. Regarding study design, most included studies were retrospective, potentially introducing selection and information biases that limit causal inference. The significant heterogeneity in study designs and patient populations may affect the consistency of our findings. Furthermore, the small number of studies reporting surgical outcomes restricted our capacity to perform comprehensive comparative analyses between surgical and non-surgical management.

Data-related limitations also impacted our analysis. The included studies predominantly reported dexamethasone suppression test results in a binary manner—either below or above 50 nmol/L—without disclosing precise cortisol measurements, constraining our ability to analyze borderline cases and nuanced hormonal responses. The assessment of aldosterone and renin levels was limited to baseline measurements, without follow-up monitoring or screening for primary hyperaldosteronism in patients with non-functional tumors. Additionally,

limited baseline tumor measurement data prevented detailed analysis of growth patterns in relation to initial tumor size.

Our analytical capabilities were further restricted by several factors. The relatively small number of available studies and population heterogeneity limited our ability to conduct comprehensive subgroup analyses. For most outcomes, the limited number of studies (fewer than eight) prevented reliable publication bias assessment using funnel plots, and even for our largest analysis groups, the relatively small sample size precluded reliable statistical adjustments for publication bias. Despite conducting quality assessment using a modified Newcastle–Ottawa Scale, the predominance of medium-quality retrospective studies limited our ability to determine how methodologically stronger or larger studies might influence our findings. Due to inconsistent reporting in the primary literature, we were unable to meta-analyze data on metabolic syndrome as a composite outcome in patients with non-functioning adrenal incidentalomas. Similarly, none of the included studies specifically measured insulin resistance parameters (such as HOMA-IR), representing an important gap in current evidence. Most original studies lacked appropriate control groups and could not be adjusted for age as a potential confounding factor, limiting our ability to establish clear temporal relationships between adrenal incidentalomas and subsequent metabolic complications. The exploration of metabolic impacts in unilateral versus bilateral adrenal incidentals was not possible due to data limitations.

Regarding result interpretation, variations in follow-up durations and inconsistent definitions of metabolic disorders across studies might have influenced the reported prevalence rates. Moreover, we could not fully assess publication bias in certain analyses due to the limited number of available studies. These limitations collectively emphasize the need for future research with standardized methodologies, comprehensive hormonal assessments, and consistent outcome definitions to better understand the metabolic implications of NFAI.

Conclusions

In patients with NFAI, subtle hormone secretion may exist despite current diagnostic criteria suggesting non-functionality. Such tumors show significant associations with metabolic disorders, particularly diabetes mellitus and dyslipidemia. Future research should focus on developing more sensitive diagnostic methods and establishing evidence-based surgical intervention criteria through prospective studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01923-2.

Supplementary Material 1.

PRISMA registration
Our meta-analysis followed a pre-established protocol based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA registration number CRD42023483006) guidelines.

Disclosure statement
The authors have nothing to disclose.

Clinical trial number
Not applicable.

Authors' contributions
All author had full access to all the data in the study and Wei Lin take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Xiaolan Li, Gang Chen and Wei Lin. Acquisition, analysis or interpretation of data: Xiaolan Li and Xinying Lin. Draft of the manuscript: Xiaolan Li, Huiyu Lan and Wei Li. Critical revision of the manuscript for important intellectual content: Huibin Huang, Junping Wen, Gang Chen and Wei Lin and. Statistical analysis: Huiyu Lan and Xinying Lin. Supervision: Gang Chen and Wei Lin.

Funding
This work was supported by Fujian Research and Training Grants for Young and Middle-aged Leaders in Healthcare (Grant No. (2023)417#), the Natural Science Foundation of Fujian Province (Grant No. 2022J011017), Fujian Joint Fund for Scientific and Technological Innovation Projects (Grant No. 2023Y9295), Department of Endocrinology (National Clinical Key Specialty, Grant No. 2023001), and Fujian Provincial Clinical Research Center for Type 2 Diabetes (Grant No. 2022Y2013).

Data availability
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 4 December 2024 Accepted: 2 April 2025
Published online: 07 April 2025

References

1. Fassnacht M, Arlt W, Bancos I, Dralle H, Newell-Price J, Sahdev A, Tabarin A, Terzolo M, Tsagarakis S, 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(2):G1–g34.
2. Ebbehoj A, Li D, Kaur RJ, Zhang C, Singh S, Li T, Atkinson E, Achenbach S, Khosla S, Arlt W, et al. Epidemiology of adrenal tumours in Olmsted

County, Minnesota, USA: a population-based cohort study. Lancet Diabetes Endocrinol. 2020;8(11):894–902.
3. Fassnacht M, Tsagarakis S, Terzolo M, Tabarin A, Sahdev A, Newell-Price J, Pelsma I, Marina L, Lorenz K, Bancos I, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2023;189(1):G1–42.
4. Elhassan YS, Alahdab F, Prete A, Delivanis DA, Khanna A, Prokop L, Murad MH, O'Reilly MW, Arlt W, Bancos I. Natural history of adrenal incidentalomas with and without mild autonomous cortisol excess a systematic review and meta-analysis. Ann Internal Med. 2019;171(2):107-+.
5. Athanasouli F, Georgiopoulos G, Asonitis N, Petychaki F, Savelli A, Panou E, Angelousi A. Nonfunctional adrenal adenomas and impaired glucose metabolism: a systematic review and meta-analysis. Endocrine. 2021;74(1):50–60.
6. Remde H, Kranz S, Morell SM, Altieri B, Kroiss M, Detomas M, Fassnacht M, Deutschbein T. Clinical course of patients with adrenal incidentalomas and cortisol autonomy: a German retrospective single center cohort study. Front Endocrinol (Lausanne). 2023;14:1123132.
7. Xu TY, Xia LL, Wang XJ, Zhang XH, Zhong S, Qin L, Zhang X, Zhu Y, Shen ZJ. Effectiveness of partial adrenalectomy for concomitant hypertension in patients with nonfunctional adrenal adenoma. Int Urol Nephrol. 2015;47(1):59–67.
8. Wang J, Zhu Y, Wang Z, Liu C, Liu S, Li X, Chen R, Zhan Y, Wang S, Zeng X. Hypertension Resolution after Laparoscopic Adrenal Tumor Resection in Patients of Adrenal Incidentaloma with Normal Hormone Levels. Urol Int. 2023;107(2):193–201. https://doi.org/10.1159/000524803. Epub 2022 Jun 7. PMID: 35671712.
9. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700.
10. Zhu Z, Zeng Q, Liu Q, Wen J, Chen G. Association of glucose-lowering drugs with outcomes in patients with diabetes before hospitalization for COVID-19: a systematic review and network meta-analysis. JAMA Netw Open. 2022;5(12):e2244652.
11. Ruppar T. Meta-analysis: How to quantify and explain heterogeneity? Eur J Cardiovasc Nurs. 2020;19(7):646–52.
12. Lan H, Wen J, Mao Y, Huang H, Chen G, Lin W. Combined T4 + T3 therapy versus T4 monotherapy effect on psychological health in hypothyroidism: a systematic review and meta-analysis. Clin Endocrinol (Oxf). 2022;97(1):13–25.
13. Ou X, Jiang J, Lin B, Liu Q, Lin W, Chen G, Wen J. Antibody responses to COVID-19 vaccination in people with obesity: a systematic review and meta-analysis. Influenza Other Respir Viruses. 2023;17(1):e13078.
14. Mao Y, Lin W, Wen J, Chen G. Impact and efficacy of mobile health intervention in the management of diabetes and hypertension: a systematic review and meta-analysis. BMJ Open Diabetes Res Care. 2020;8(1):e001225.
15. Jennions MD, Møller AP. Publication bias in ecology and evolution: an empirical assessment using the "trim and fill" method. Biol Rev Camb Philos Soc. 2002;77(2):211–22.
16. Zhu Z, Mao Y, Chen G. Predictive value of HbA1c for in-hospital adverse prognosis in COVID-19: a systematic review and meta-analysis. Prim Care Diabetes. 2021;15(6):910–7.
17. Podbregar A, Kocjan T, Rakusa M, Popovic P, Garbajs M, Goricar K, Janez A, Jensterle M. Natural history of nonfunctioning adrenal incidentalomas: a 10-year longitudinal follow-up study. Endocr Connect. 2021;10(6):637–45.
18. Araujo-Castro M, Ramirez PP, Lazaro CR, Centeno RG, Gimeno PG, Fernandez-Ladreda MT, Nunez MAS, Marazuela M, Escobar-Morreale HF, Valderrabano P. Predictors of tumour growth and autonomous cortisol secretion development during follow-up in non-functioning adrenal incidentalomas. J Clin Med. 2021;10(23):5509.
19. Falcetta P, Orsolini F, Benelli E, Agretti P, Vitti P, Di Cosmo C, Tonacchera M. Clinical features, risk of mass enlargement, and development of endocrine hyperfunction in patients with adrenal incidentalomas: a long-term follow-up study. Endocrine. 2021;71(1):178–88.
20. Ruiz A, Michalopoulou T, Megia A, Näf S, Simón-Muela I, Solano E, Martínez L, Vendrell J. Accuracy of new recommendations for adrenal incidentalomas in the evaluation of excessive cortisol secretion and follow-up. Eur J Clin Invest. 2019;49(2):e13048.
21. Hong AR, Kim JH, Park KS, Kim KY, Lee JH, Kong SH, Lee SY, Shin CS, Kim SW, Kim SY. Optimal follow-up strategies for adrenal incidentalomas: reappraisal of the 2016 ESE-ENSAT guidelines in real clinical practice. Eur J Endocrinol. 2017;177(6):475–83.
22. Patrova J, Kjellman M, Wahrenberg H, Falhammar H. Increased mortality in patients with adrenal incidentalomas and autonomous cortisol secretion: a 13-year retrospective study from one center. Endocrine. 2017;58(2):267–75.
23. Papanastasiou L, Alexandraki KI, Androulakis II, Fountoulakis S, Kounadi T, Markou A, Tsiavos V, Samara C, Papaioannou TG, Piaditis G, et al. Concomitant alterations of metabolic parameters, cardiovascular risk factors and altered cortisol secretion in patients with adrenal incidentalomas during prolonged follow-up. Clin Endocrinol (Oxf). 2017;86(4):488–98.
24. Vasilev V, Matrozova J, Elenkova A, Zacharieva S. Clinical characteristics and follow-up of incidentally found adrenal tumours - results from a single tertiary centre. Cent Eur J Med. 2014;9(2):292–301.
25. Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, Mosconi C, Golfieri R, Paccapelo A, Pagotto U, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. 2014;2(5):396–405.
26. Ng VW, Ma RC, So WY, Choi KC, Kong AP, Cockram CS, Chow CC. Evaluation of functional and malignant adrenal incidentalomas. Arch Intern Med. 2010;170(22):2017–20.
27. Yener S, Ertilav S, Secil M, Akinci B, Demir T, Comlekci A, Yesil S. Prospective evaluation of tumour size and hormone secretion in adrenal incidentalomas. Endocr Abstr. 2010;20:P53.
28. Giordano R, Marinazzo E, Berardelli R, Picu A, Maccario M, Ghigo E, Arvat E. Long-term morphological, hormonal, and clinical follow-up in a single unit on 118 patients with adrenal incidentalomas. Eur J Endocrinol. 2010;162(4):779–85.
29. Vassilatou E, Vryonidou A, Michalopoulou S, Manolis J, Caratzas J, Phenekos C, Tzavara I. Hormonal activity of adrenal incidentalomas: results from a long-term follow-up study. Clin Endocrinol. 2009;70(5):674–9.
30. Vilar L, Freitas MDC, Canadas V, Albuquerque JL, Botelho CA, Egito CS, Arruda MJ, Silva LME, Coelho CE, Casulari LA, et al. Adrenal incidentalomas: diagnostic evaluation and long-term follow-up. Endocr Pract. 2008;14(3):269–78.
31. Xia WJ, Li Z, Li Q, Wang JW, Niu ZH. Adrenalectomy improves hypertension control in patients with non-functional adrenal adenomas without causing endocrinological changes. Int J Clin Exp Med. 2016;9(11):22296–302.
32. Bernini G, Moretti A, Iacconi P, Miccoli P, Nami R, Lucani B, Salvetti A. Anthropometric, haemodynamic, humoral and hormonal evaluation in patients with incidental adrenocortical adenomas before and after surgery. Eur J Endocrinol. 2003;148(2):213–9.
33. Remde H, Kranz S, Morell SM, Altieri B, Kroiss M, Detomas M, Fassnacht M, Deutschbein T. Clinical course of patients with adrenal incidentalomas and cortisol autonomy: a German retrospective single center cohort study. Front Endocrinol. 2023;14:1123132.
34. Yener S, Ertilav S, Secil M, Akinci B, Demir T, Kebapcilar L, Yesil S. Increased risk of unfavorable metabolic outcome during short-term follow-up in subjects with nonfunctioning adrenal adenomas. Med Princ Pract. 2012;21(5):429–34.
35. Lopez D, Luque-Fernandez MA, Steele A, Adler GK, Turchin A, Vaidya A. "Nonfunctional" adrenal tumors and the risk for incident diabetes and cardiovascular outcomes: a cohort study. Ann Intern Med. 2016;165(8):533–42.
36. Androulakis II, Kaltsas GA, Kollias GE, Markou AC, Gouli AK, Thomas DA, Alexandraki KI, Papamichael CM, Hadjidakis DJ, Piaditis GP. Patients with apparently nonfunctioning adrenal incidentalomas may be at increased cardiovascular risk due to excessive cortisol secretion. J Clin Endocrinol Metab. 2014;99(8):2754–62.
37. Comlekci A, Yener S, Ertilav S, Secil M, Akinci B, Demir T, Kebapcilar L, Bayraktar F, Yesil S, Eraslan S. Adrenal incidentaloma, clinical, metabolic, follow-up aspects: single centre experience. Endocrine. 2010;37(1):40–6.
38. Ermetici F, Dall'Asta C, Malavazos AE, Coman C, Morricone L, Montericcio V, Ambrosi B. Echocardiographic alterations in patients

with non-functioning adrenal incidentaloma. J Endocrinol Invest. 2008;31(6):573–7.
39. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome–a new worldwide definition. Lancet. 2005;366(9491):1059–62.
40. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. Clin Endocrinol (Oxf). 2006;64(4):355–65.

Publisher's Note