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Systematic Review and Meta Analysis

Comorbidities in mild autonomous cortisol secretion and the effect of treatment: systematic review and meta-analysis

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Abstract

Objective: To assess (1) comorbidities associated with and (2) treatment strategies for patients with adrenal incidentalomas and mild autonomous cortisol secretion (MACS; > 1.8 µg/dL (>50 nmol/L) cortisol level cut-off following the 1 mg dexamethasone suppression test).

Design: Systematic review and meta-analysis.

Methods: Seven databases were searched up to July 14, 2022. Eligible studies were (randomized) trials, cohort studies, and cross-sectional studies assessing comorbidities potentially attributable to cortisol excess or mortality in patients with adrenal incidentaloma with or without MACS or the effects of conservative or surgical management of MACS. Random-effects meta-analysis was performed to estimate pooled proportions (with 95% CIs).

Results: In 30 cross-sectional and 16 cohort studies ($n = 17\,156$ patients in total), patients with MACS had a higher prevalence of diabetes (relative risk [RR] 1.44 [1.23-1.69]), hypertension (RR = 1.24 [1.16-1.32]), and dyslipidemia (RR = 1.23 [1.13-1.34]). All-cause mortality (adjusted for confounders) in patients with MACS, assessed in 4 studies ($n = 5921$), was increased (hazard ratio [HR] = 1.54 [1.27-1.81]). Nine observational studies ($n = 856$) and 2 randomized trials ($n = 107$) suggest an improvement in glucometabolic control (RR = 7.99 [2.95-21.90]), hypertension (RR = 8.75 [3.99-19.18]), and dyslipidemia (RR = 3.24 [1.19-8.82]) following adrenalectomy.

Conclusions: The present systematic review and meta-analysis highlight the relevance of MACS, since both cardiometabolic morbidities and mortality appeared to have increased in patients with MACS compared to patients with non-functioning incidentalomas. However, due to heterogeneous definitions, various outcomes, selective reporting, and missing data, the reported pooled estimates need to be interpreted with caution. The small number of patients in randomized trials prevents any strong conclusion on the causality between MACS and these comorbidities.

Keywords: adrenal adenoma, cortisol, mild autonomous cortisol secretion, comorbidities, systematic review

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Significance

This systematic review of 46 clinical studies including more than 17 000 patients provides evidence for the association of mild autonomous cortisol secretion (MACS) in patients with adrenal incidentaloma with increased all-cause mortality and increased risk for cardiometabolic comorbidities, for example, hypertension and diabetes. There is a suggestion that the cardiometabolic profile improves after surgery for MACS, although the number of treated patients in interventional studies is small. The presented data have informed the European Society of Endocrinology-European Network for the Study of Adrenal Tumors (ESE-ENSAT) clinical practice guideline on adrenal incidentalomas, which is published in parallel.

Introduction

The term mild autonomous cortisol secretion (MACS) was proposed by the recent clinical guidelines from the European Society of Endocrinology (ESE) and the European Network for the Study of Adrenal Tumors (ENSAT) for patients with adrenal incidentalomas and adrenocorticotropic hormone (ACTH)-independent cortisol hypersecretion without clinical signs of overt Cushing's syndrome (eg, catabolic symptoms such as muscle weakness, skin fragility, and striae).[1,2] In this condition, cortisol production is independent of physiological hypothalamic–pituitary–adrenal (HPA) axis feedback mechanisms resulting in longstanding inappropriate exposure to cortisol in various organs and tissues.[3] Overt Cushing's syndrome—caused by ACTH-dependent hypercortisolism—is associated with several comorbidities, including hypertension, diabetes, and an increased fracture risk.[4-8] Moreover, cortisol hypersecretion is associated with an increased mortality risk.[9-14] However, the association between MACS and these comorbidities potentially attributable to cortisol is uncertain, and the causality is disputed.

There is considerable discussion regarding optimal testing and relevant cut-offs to diagnose MACS. The overnight 1 mg dexamethasone suppression test (1mg-DST) is considered the best, although suboptimal, test.[1,2] Various diagnostic algorithms have been used for "subclinical hypercortisolism," although direct comparisons of diagnostic performance of tests are lacking. Importantly, formal comparisons between algorithms and relevant clinical outcomes are lacking. In the 2016 ESE-ENSAT guideline, the use of the 1mg-DST was recommended based on pathophysiological reasoning, simplicity, and the incorporation of the 1mg-DST in the diagnostic algorithms of most studies.[1] Given the available evidence at that time, the guidelines proposed 2 categories depending on the post-1mg-DST cortisol levels: "autonomous cortisol secretion" for cortisol levels >138 nmol/L and "possible autonomous cortisol secretion" for cortisol levels 51-138 nmol/L. During the development of the updated guideline, the cut-off of >50 nmol/L was evaluated and therefore included in the present review.[1,2]

Furthermore, the optimal therapeutic approach for MACS is not well established. Two approaches are considered: (1) management of MACS-associated comorbidities (eg, diabetes and hypertension) and (2) adrenalectomy. The present study aims to systematically review the literature regarding (1) the epidemiological scope of comorbidities in MACS and (2) the effect of treatment, either conservative, medical, or surgical, on the aforementioned comorbidities.

Methods

Research questions and study aims

The present systematic reviews and meta-analyses are incorporated in the 2023 ESE-ENSAT adrenal incidentaloma guideline.[2] For the present review, 2 research questions were formulated: (1) Is MACS associated with an increased cardiovascular, metabolic, and fracture risk in patients with adrenal mass(es)?, and (2) What is the effectiveness of surgery versus conservative/medical treatment in patients with adrenal mass(es) and MACS with an increased cardiovascular, metabolic, and fracture risk? Two separate systematic reviews of the literature were performed to answer these questions. These reviews were performed while adhering to the Declaration of Helsinki. Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15] The present reviews were not registered on PROSPERO, as they were part of the clinical practice guideline development. The present reviews were not assessed by the medical ethical review committee as no individual patients were studied.

Eligibility criteria

Original studies on patients with adrenal mass(es), in which endocrine work-up for glucocorticoid excess was performed —irrespective of definitions of "autonomous cortisol secretion" used—were eligible for inclusion. Comparison between patients based on biochemical profiles (including post-1mg-DST serum cortisol levels) needed to be incorporated.

For the first systematic review (Q1), comparing patients with non-functioning adrenal incidentaloma and patients with adrenal incidentaloma and MACS, cross-sectional studies and longitudinal clinical studies (ie, randomized or non-randomized trials and cohort studies) assessing at least one of the following clinically relevant outcomes were eligible: mortality, cardiovascular events, cardiometabolic comorbidities (eg, glucose intolerance, diabetes mellitus, hypertension, and dyslipidemia), vertebral fractures, and health-related quality of life (HR-QoL).

For the second systematic review (Q2), comparing conservative (ie, active surveillance or pharmacological interventions) versus surgical approaches in patients with adrenal incidentaloma and MACS, longitudinal clinical studies (ie, randomized or non-randomized trials and cohort studies) assessing at least one of the following major outcomes were eligible: mortality, cardiovascular events, cardiometabolic comorbidities, vertebral fractures, and HR-QoL.

To minimize risk of selection bias, ≥ 10 patients per study arm had to be included. Only articles written in English were considered.

Definition of MACS

Following the cut-offs suggested in the 2016 and revised ESE-ENSAT guideline, 3 main groups based on cortisol after 1mg-DST were defined: (1) serum cortisol ≤50 nmol/L (≤1.8 µg/dL) as absence of autonomous cortisol secretion, (2) serum cortisol 51-138 nmol/L (1.9-5.0 µg/dL) as "possible

autonomous cortisol secretion," and (3) serum cortisol >138 nmol/L (>5.0 µg/dL) as autonomous cortisol secretion. However, not all studies used these exact criteria. These definitions were applied as accurately as possible. Additionally, separate analyses were performed discriminating 2 patient groups: (1) serum cortisol ≤50 nmol/L (≤1.8 µg/dL) and (2) serum cortisol >50 nmol/L (>1.8 µg/dL).

Search strategy

PubMed; Embase; Web of Science; Cochrane Library (CENTRAL); Cochrane Library—Cochrane Database of Systematic Reviews; NHS Economic Evaluation Database (NHSEED); and Database of Abstracts of Reviews of Effects (DARE) were systematically searched in 2015 for the first guideline version and updated on July 14, 2022, in cooperation with a specialized librarian. Furthermore, references of included articles, as well as screened studies found using the searches of the other systematic reviews performed for the adrenal incidentaloma guideline update, were assessed to increase the number of potentially eligible articles. The search strategies for the systematic reviews are shown in File S1, and File S2, respectively.

Data extraction and study outcomes

Identified references were entered in EndNote X20 (Thomson Reuters, Philadelphia, PA, USA). First, studies were screened by title and abstract, followed by the full-text screening of all eligible articles. Two independent reviewers (I.C.M.P. and O.M.D.) reviewed potentially relevant articles in detail. Following full-text screening, data were extracted from included studies.

The following data were extracted: study design, number of patients, study population, study period, eligibility criteria, subgroups based on biochemical profiles or treatment strategies, follow-up duration, and outcome parameters (number of patients/events per group and effect sizes). In some studies, data were solely presented as percentages (resulting in back-calculation of absolute numbers for that outcome), or solely presented in figures without mentioning absolute patient numbers (resulting in the estimation of the numbers to the best of the author's abilities). If data were presented only according to patient categories (eg, pre-, and post-menopausal women), the data were combined prior to analyses. For the second systematic review, improvement or complete resolution of the assessed comorbidities was recorded. For the assessment of improvement, all reported data (ie, absolute numbers, as well as general statements without further specification) were extracted and considered.

Reported effect estimates adjusted for confounders were extracted as well. Unfortunately, uncorrected effect sizes (bar the outcomes of mortality) were used for further analyses, since not all studies performed correction for (multiple) confounding factors. For the HR-QoL outcomes, absolute values as outcomes of the validated questionnaires were extracted.

Risk of bias assessment using Grading of Recommendations, Assessment, Development, and Evaluations

Risk of bias and evidence quality assessment was performed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE).[16-18] In Tables S1 and S2, all components of the GRADE system (ie, imprecision, inconsistency, indirectness, and publication bias, respectively) and the final grading of all outcomes are summarized.

Statistical analysis

An overview of reported outcomes of all included studies is summarized in Table S3 (for question 1) and Table S4 (for question 2), respectively. If multiple studies described (partially) overlapping populations, only the largest study reporting on the outcome of interest was included, resulting in the meta-analyses containing a subset of the included studies for both question 1 and question 2. A random-effects logistic regression model was used for pooled percentages and relative risks (RR), accompanied by 95% CIs. In order to prevent exclusion of studies with 0 events, results were modified to include 0.5 events. Subgroup analyses based on type of study (cohort study *vs* randomized controlled trial [RCT]), and cut-off levels were performed. All analyses were performed using Stata 16.1 (Stata Corp., College Station, TX, United States).

Results

Study inclusion

The flowcharts of study inclusion for the 2 systematic reviews are shown in Figure 1. The initial search yielded 1059 abstracts (Q1) and 291 abstracts (Q2) respectively, of which 52 (Q1) and 8 (Q2) publications were assessed in detail. A total of 46 (34 new) studies for Q1 (comorbid conditions based on biochemical cortisol profile) and 11 studies (7 new) for Q2 (therapeutic approaches for patients with autonomous cortisol secretion) were included.

Description of included studies

Included studies were published between 2004 and 2022. The predominant method used to define MACS was cortisol levels >1.8 µg/dL post-1mg-DST, especially in studies published after publication of the 2016 guideline.[1]

Comorbid conditions in MACS (question 1)

Forty-six studies (34 newly included) were included with a total number of 17 156 patients (6339 patients with MACS and 10 817 patients with non-functioning adenomas): 30 cross-sectional (23 newly included)[19-48] and 16 cohort studies (11 newly included).[11,49-64] The summary of included studies is listed in Table S3. In the cross-sectional studies, the risk of bias is considered high, given the inability to assess causality and the potential for residual confounding (see Table S1). Differences in diagnostic protocols, definitions of outcome, and duration of follow-up were associated with considerable heterogeneity.

Treatment of MACS (question 2)

Eleven studies with a total number of 856 patients with MACS (475 patients treated by adrenalectomy and 381 patients not treated surgically) were included: 2 RCT,[65,66] and 9 observational studies.[60,64,67-73] The summary of included studies is listed in Table S4. The conservative treatment modalities ranged from pharmacotherapeutic interventions for comorbidities to watchful waiting, with different approaches not being standardized. The quality of evidence from these studies is low to very low, mainly due to confounding factors (as outlined in Table S2). Two studies were randomized,

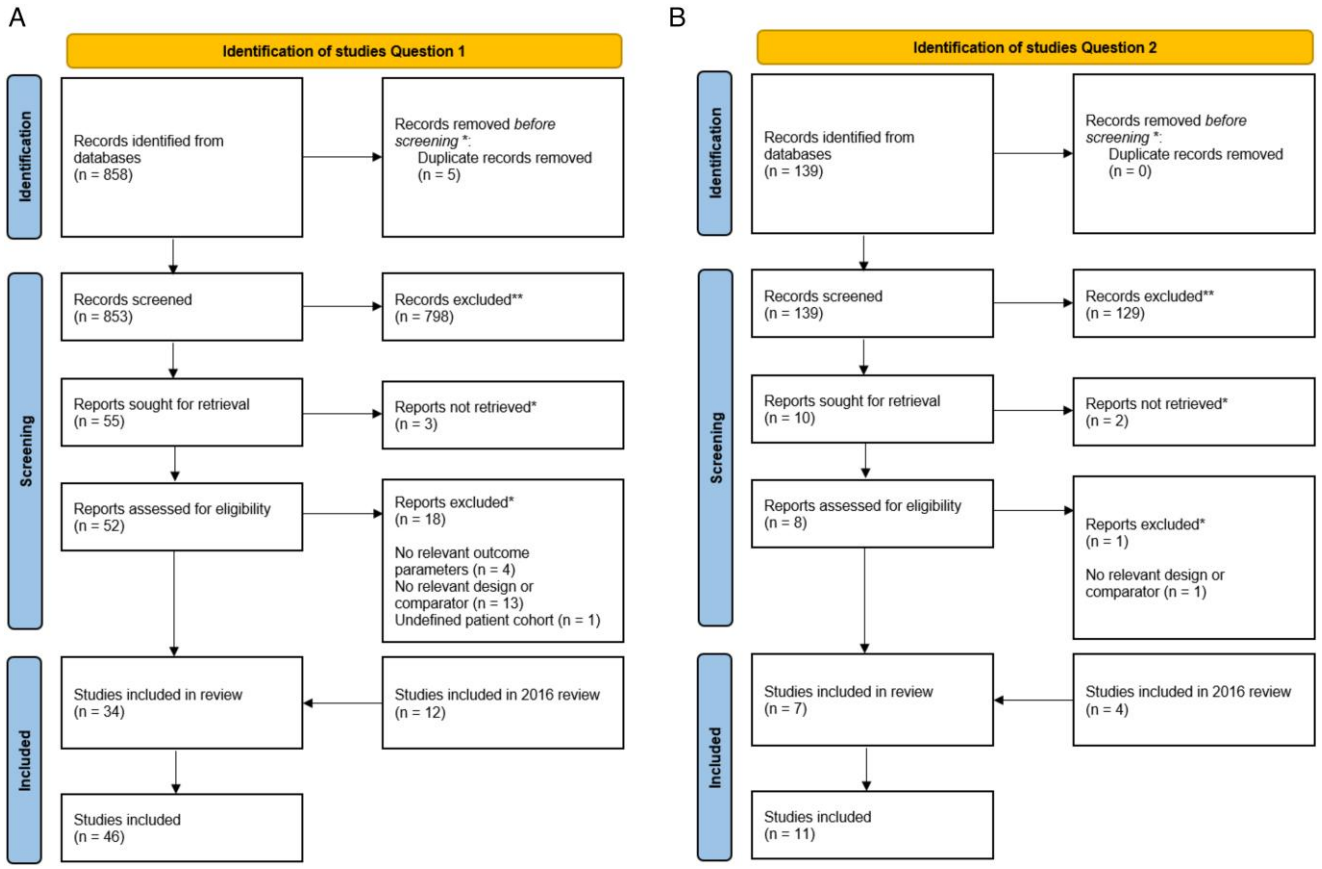

Figure 1. Flowchart of article inclusion. All articles derived from the searches for question 1 (A) and question 2 (B) were screened based on title and abstract, followed by full-text screening when applicable. n, number of articles.

although treatment allocation was not concealed, and none of the studies reported blinded outcome assessment.[65,66] Furthermore, most studies were downgraded for imprecision, due to the small number of events. Differences in diagnostic protocols used to define autonomous cortisol secretion, definitions of outcomes, and duration of follow-up were heterogeneous between and within studies. Moreover, in none of these 11 included studies, evaluation and treatment of concomitant comorbidities following intervention were standardized.

Clinical conditions in autonomous cortisol secretion (question 1)

Mortality

Six studies reported on all-cause mortality.[11,49,55,56,59,62] In one study,[49] analyses performed were not adjusted for confounding factors, and therefore, not included in further analyses. In another study, solely reporting on absolute cortisol levels, a significantly increased hazard ratio (HR) for mortality was observed with every 10 nmol/L increase in cortisol levels following 1mg-DST (HR = 1.10 [95% CI 1.01-1.19]).[11] The remaining 4 studies (including 5921 patients) are summarized in Figure 2, with all point estimates being >1.0 regardless of the cut-off levels used for the definition of MACS and pooled HR being increased in patients with MACS (1mg-DST cortisol level cut-off of >1.8 µg/dL): HR = 1.54 (95% CI 1.27-1.81).[55,56,59,62] The leading causes of death were cardiovascular[11,49,56] and malignancies.[55,59]

Cardiovascular events

Twelve studies (6 cross-sectional studies and 6 cohort studies) reported on the prevalence or incidence of acute cardiovascular events,[11,36,41,52,53,55,56,60,61] with different definitions of cardiovascular events being used (eg, myocardial infarction and stroke). Using cortisol levels >1.8 µg/dL following 1mg-DST, point estimates for the prevalence of cardiovascular events were >1.0 in 3/4 studies comparing patients with MACS and non-functioning adenomas, whereas point estimates for CVA and MI varied greatly (Figure S1). In 5 cohort studies,[11,52,53,55,56] the incidence of cardiovascular events during follow-up was higher in MACS.

Metabolic and cardiovascular comorbidities

Measures of glucose intolerance and insulin resistance were assessed in 30 studies (21 cross-sectional and 9 cohort studies).[22,23,25,26,28-36,38,39,41-45,48,50,52,54-56,58,60,61,64] In 19/20 studies assessing the prevalence of diabetes, the point estimates were >1.0, indicating an increased prevalence of diabetes mellitus in patients with MACS compared to non-functioning adenomas. Conclusively, pooled prevalence of diabetes was increased in patients with impaired cortisol suppression (1mg-DST cortisol level >1.8 µg/dL): RR = 1.44 (95% CI 1.23-1.69).[26,29,30,35,36,38,41,42,45,55,56,58,60,61] However, there was no "concentration dependence" when 2 different cut-off levels for the DST were analyzed (Figure 3). During follow-up of patients with MACS (ranging from 2 to 6.9 years), the risk of developing type 2 diabetes mellitus was

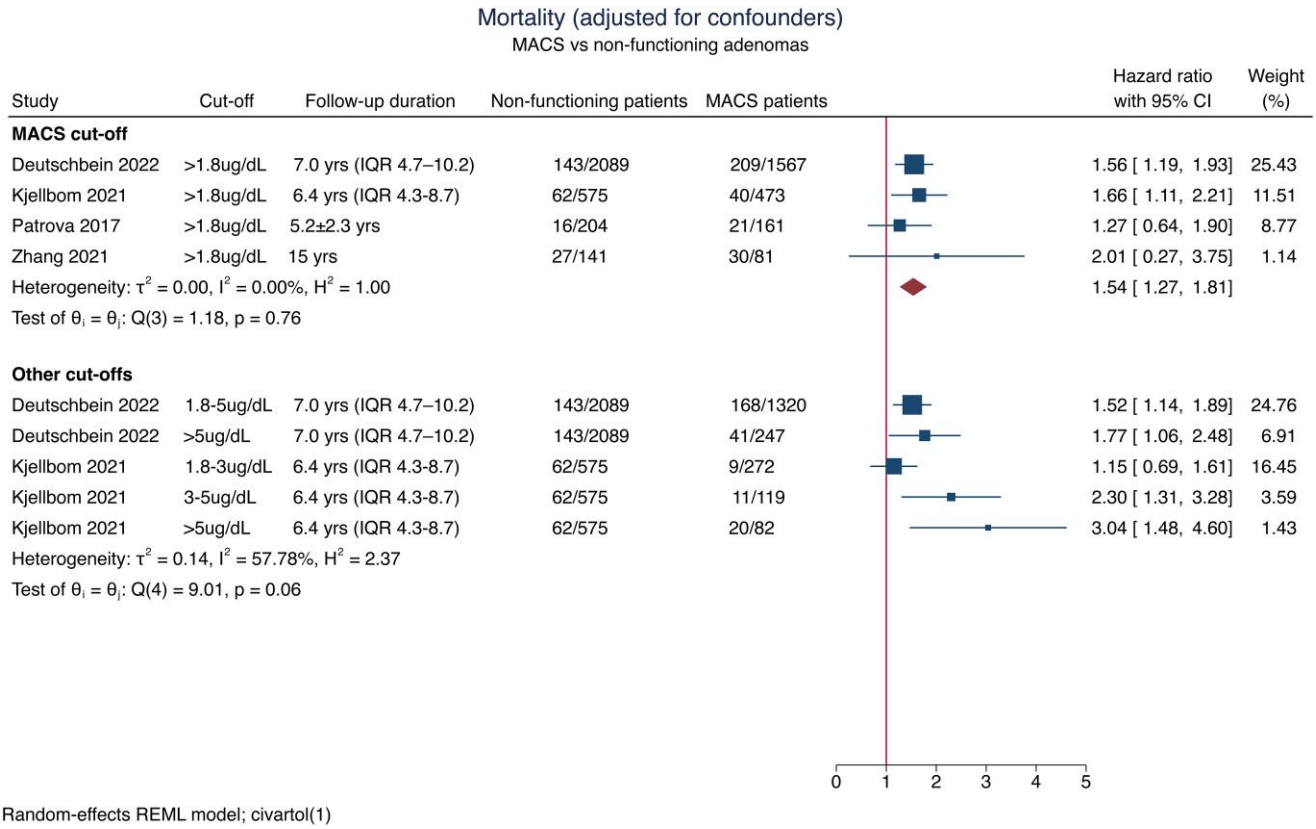

Figure 2. Meta-analysis of all-cause mortality in patients with adrenal incidentaloma. HR with CIs for all-cause mortality as reported by the individual studies, following adjustment for >2 confounders were included. Because of the asymmetry in the reported CIs, the CI tolerance was adjusted for performance of the random-effects maximum likelihood (REML) meta-analysis of the HR. The squares and horizontal lines correspond to the HR with the adjusted 95% CIs. The diamond represents the pooled HR and 95% CI based on the 1mg-DST cut-off of >1.8 µg/dL (50 nmol/L) for MACS. The reference line represents the estimate of 1.0 meaning no difference between the patient groups. MACS, mild autonomous cortisol secretion.

not increased in MACS compared to non-functioning adrenal adenomas.[50,52,54,58]

In 31 studies (22 cross-sectional and 9 cohort studies), the prevalence or incidence of hypertension in patients with MACS was reported.[26,28-36,38,39,41,42,44,45,47,48,50,52,54-56,58,61] In 25/26 studies, the point estimates were >1.0, indicating an increased hypertension prevalence in MACS. Pooled RR (1mg-DST cortisol level >1.8 µg/dL) of hypertension was higher in MACS: RR = 1.24 (95% CI 1.16-1.32), but again no "concentration dependency" was present (Figure 4). Development of hypertension or worsened control of blood pressure (BP) during follow-up (range 24-83 months) was assessed in 3 studies and was not clearly associated with MACS.[50,52,54]

Dyslipidemia was reported in 22 studies (17 cross-sectional and 5 cohort studies).[26,28-36,38,39,41-44,47,50,54,55,58,64] In 15/19 studies, point estimates were >1.0, indicating an increased risk for the prevalence of dyslipidemia in MACS. Pooled RR of prevalent dyslipidemia (1mg-DST cortisol level >1.8 µg/dL) was higher in patients with MACS: namely, RR = 1.23 (95% CI 1.13-1.34) (Figure 5). During follow-up of ~36 months as assessed by 2 studies, no clearly increased risk for the development of dyslipidemia in patients with MACS was observed.[50,54]

Fractures

Ten studies reported on fractures.[19-21,23,27,37,38,46,51,63] In 7 studies, the prevalence of vertebral fractures in MACS was compared to non-functioning adenomas (Figure S2). Due to heterogeneity between studies regarding outcomes reported and cut-offs used for MACS, no pooled statistics were provided. In 3 studies, the prevalence of multiple types of fractures (including fragility fractures) was assessed and found to have not increased, with 2/3 studies reporting no evidence of fractures in patients with and without MACS[27,38] and 1 study reporting a RR of 1.06 (.78-1.45) for the prevalence of fractures.[63] In 2 cohort studies,[51,57] the incidence of new vertebral fractures or all types of fractures, respectively, was assessed, of which point estimates were >1.0 comparing patients with MACS to patients with non-functioning adenomas (adjusted odds ratio [OR] = 12.3 [4.1-36.5]) and unadjusted RR = 1.49 (.93-2.39).[51] Notably, most of the vertebral fractures detected in these series were asymptomatic, including microfractures detected after inspection of spinal radiographs.

HR-QoL

Two studies reported on several QoL outcomes, of which most subscales were not different between patients with MACS and patients with non-functioning adenomas,[40,48] bar the components disability and stress Sheehan Disability Scale (SDS) being higher in patients with MACS.[40] Two studies reported on mental health and cognitive function status, which was not affected by the presence of MACS, but patient frailty was significantly higher in patients with MACS compared to non-functioning adenomas (age-, BMI-, and sex-adjusted).[40,74]

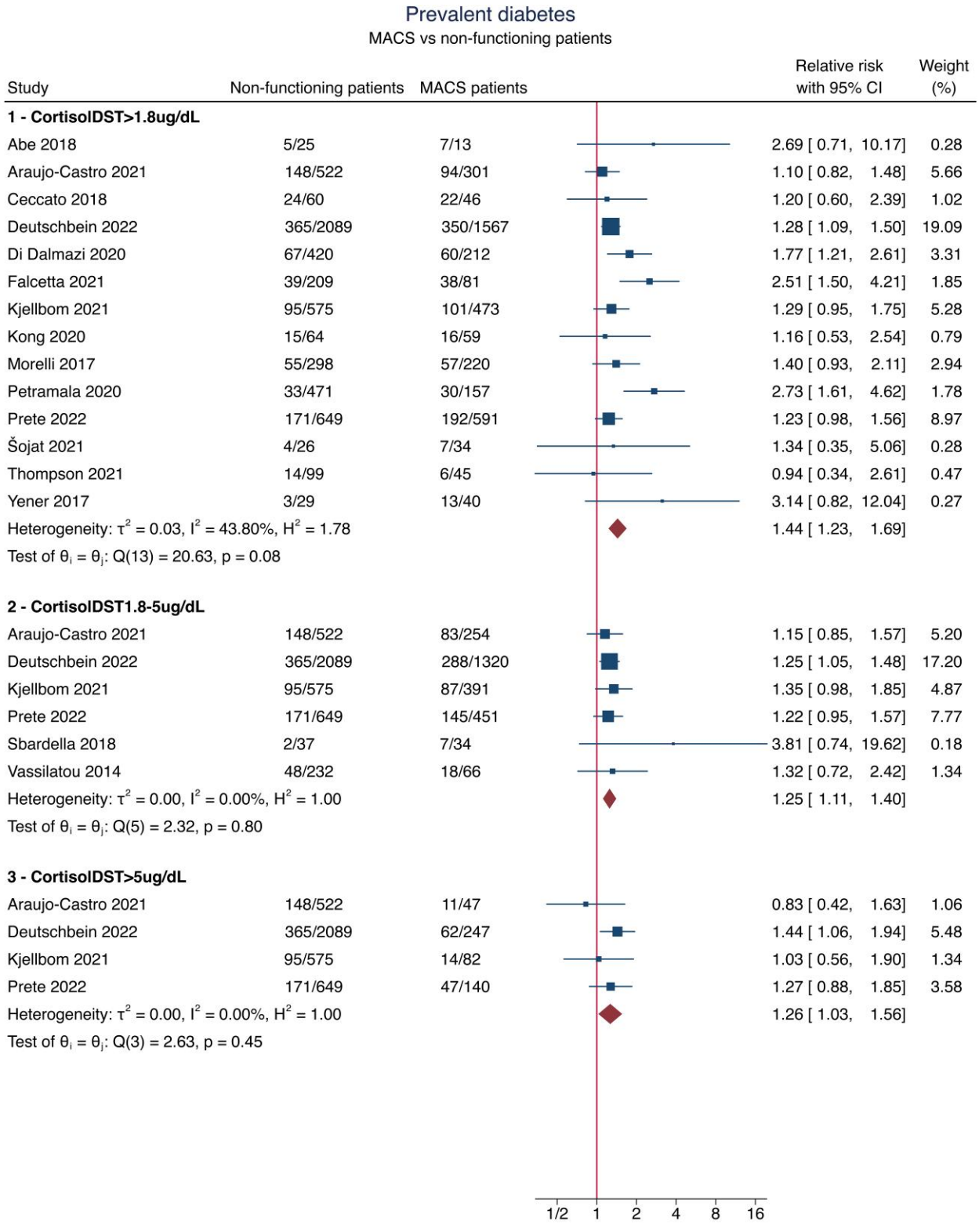

Figure 3. Summary of RR for prevalent diabetes in patients with adrenal incidentaloma comparing non-functioning adenomas to MACS. RR with CIs for the prevalence of diabetes as reported were included in the random-effects maximum likelihood (REML) meta-analysis based on the different cut-offs for MACS following the 1mg-DST. The squares and horizontal lines correspond to the RR with 95% CIs. The diamond represents the pooled HR and 95% CI. The reference line represents the estimate of 1.0 meaning no difference between the patient groups. DST, dexamethasone suppression test; MACS, mild autonomous cortisol secretion.

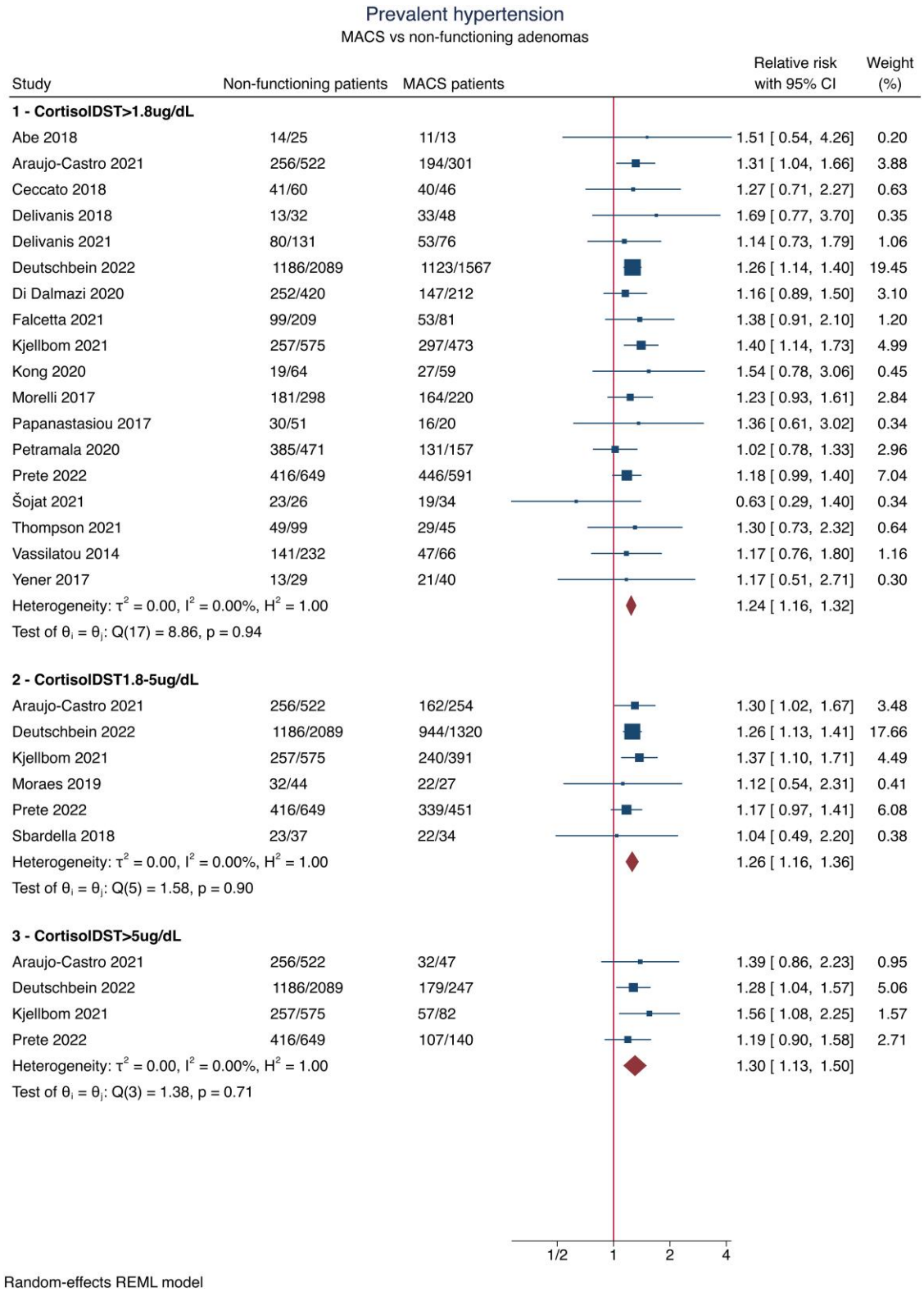

Figure 4. Summary of RR for prevalent hypertension in patients with adrenal incidentaloma comparing non-functioning adenomas to MACS. RR with CIs for the prevalence of hypertension as reported were included in the random-effects maximum likelihood (REML) meta-analysis based on the different cut-offs for MACS following the 1mg-DST. The squares and horizontal lines correspond to the RR with 95% CIs. The diamond represents the pooled HR and 95% CI. The reference line represents the estimate of 1.0 meaning no difference between the patient groups. DST, dexamethasone suppression test; MACS, mild autonomous cortisol secretion.

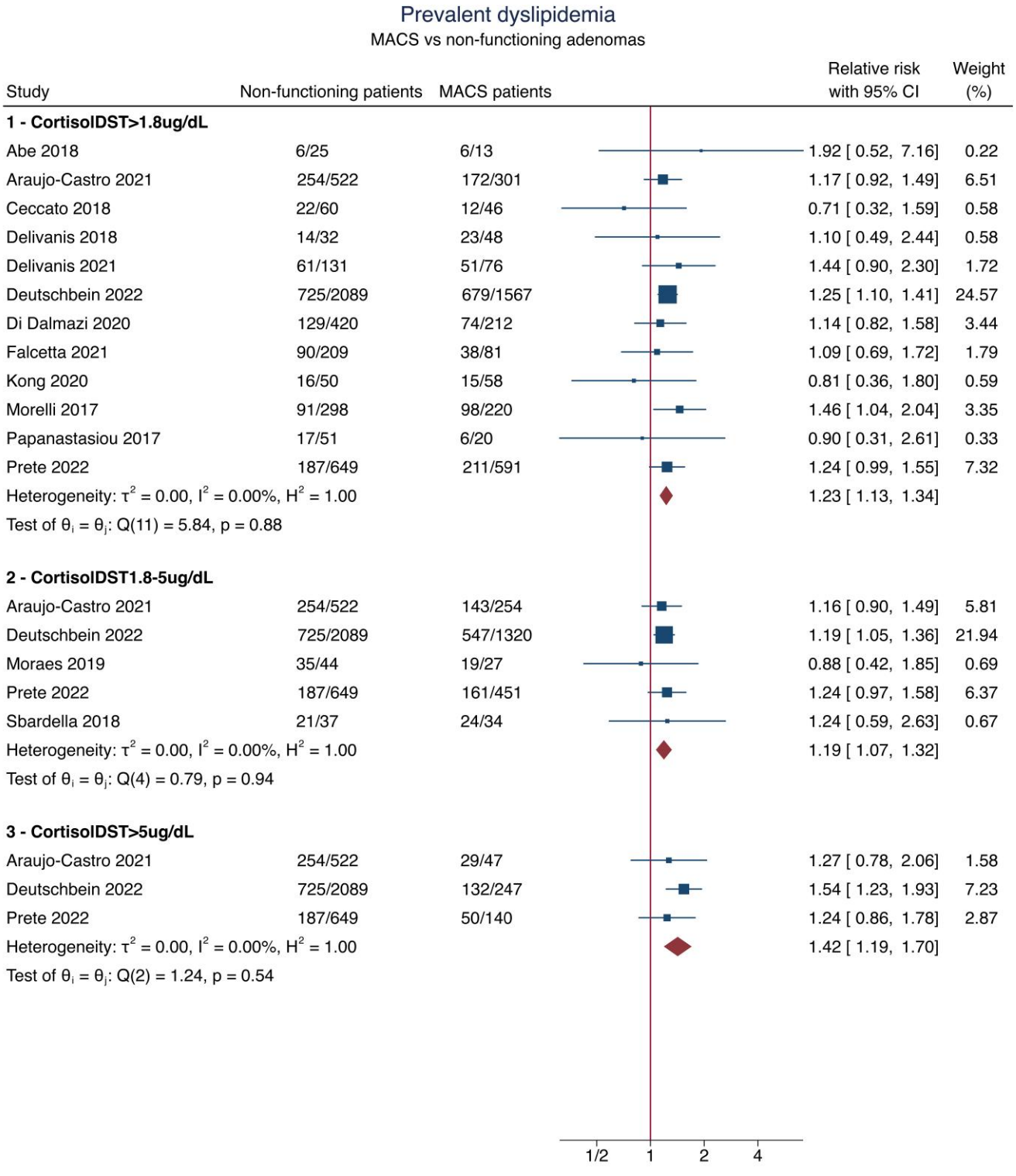

Figure 5. Summary of RR for prevalent dyslipidemia in patients with adrenal incidentaloma comparing non-functioning adenomas to MACS. RR with CIs for the prevalence of dyslipidemia as reported were included in the random-effects maximum likelihood (REML) meta-analysis based on the different cut-offs for MACS following the 1mg-DST. The squares and horizontal lines correspond to the RR with 95% CIs. The diamond represents the pooled HR and 95% CI. The reference line represents the estimate of 1.0 meaning no difference between the patient groups. DST, dexamethasone suppression test; MACS, mild autonomous cortisol secretion.

Effect of surgical treatment in MACS (question 2)

Mortality and major cardiovascular events

None of the included studies reported on the risk of mortality, or major cardiovascular events.

Metabolic and cardiovascular comorbidities

Improvement of impaired glucose tolerance or diabetes mellitus was assessed in 9 studies (2 RCTs and 7 cohort studies).[60,64-73] In the first RCT, including 45 patients in total, in 5/8 patients with type 2 diabetes mellitus, glucometabolic control improved after surgery (with normalization of glucose tolerance in 2 patients), compared to 0/6 patients with diabetes in the conservative group.[65] In the second and largest RCT to date including 62 patients in total, 56 patients could be evaluated at least 6 months after randomization. In these patients, rates of improvement in glycemic control were 28% (surgery) and 3.3% (conservative), respectively.[66] However, one has to acknowledge that only 11 patients (19.6%) had diabetes and additional 16 (28.6%) impaired fasting glucose or impaired glucose tolerance. Comparable results were reported in the cohort studies, with all included studies reporting point estimates >1.0 indicating better outcomes after surgical treatment: pooled RR = 8.0 (2.9-21.9) (Figure 6A).[67-69,71-73]

Improvement of BP control was assessed in 9 studies (2 RCTS and 7 cohort studies).[60,64-73] In the conservative treatment group, improvement of BP was only reported in 2/9 studies,[66,71] whereas in the majority of studies, the surgically treated patients showed improved BP control.[65,67-69,72,73] Notably, in the largest RCT, improvement in BP control was shown in 68% of surgically treated patients and in only 13.4% in the conservative arm;[66] again, one-third of patients did not have hypertension. As summarized in Figure 6B, all individual studies reported point estimates of >1.0 for improvement or normalization of BP following surgery, with pooled RR being 8.8 (4.0-19.2).

In 6 studies (1 RCT and 5 cohort studies), improvement of dyslipidemia was assessed.[65,67-69,72,73] Chiodini et al.[67] reported similar numbers of patients improving LDL-cholesterol levels in both treatment groups, whereas in the other studies, none of the conservatively treated patients, in contrast to the surgically treated patients, showed improvement of lipids.[65,68,69,72,73] Pooled RR for the improvement of dyslipidemia in patients with MACS was 3.2 (1.2-8.8) comparing surgery to conservative management, as is shown in Figure 6C.

Risk of vertebral fractures

Solely 1 study reported on vertebral (micro)fractures.[71] Patients who underwent adrenalectomy presented with less new vertebral (micro)fractures compared to patients managed conservatively during follow-up of 39.9 ± 20.9 months (9.4% *vs* 52.2%).

HR-QoL

In 1 study, HR-QoL was assessed using the Short Form 36 generic questionnaire.[68] Solely, the operated patients showed improvement on the SF-36 physical component scores and mental component scores (PCS and MCS, respectively) following treatment (MCS: 43.8 ± 11.8 *vs* 54.1 ± 10.1, $P = .003$; PCS: 50.9 ± 7.3 *vs* 56.7 ± 7.3, $P = .0016$), whereas the non-operated patients did not improve (MCS: 44.5 ± 10.8 *vs* 44.9 ± 12.4, $P = .78$; PCS: 51.7 ± 9.7 *vs* 50.5 ± 9.4, $P = .45$). None of the studies reported on mental health, cognitive function status, or patient frailty.

Discussion

In this systematic review, the prevalence of comorbidities potentially attributable to cortisol in patients with MACS compared to patients with non-functioning adrenal incidentalomas was assessed. Generally, the prevalence of cardiometabolic diseases was increased in patients with MACS, with the prevalence of diabetes, hypertension, and dyslipidemia being 15%-40% higher compared to patients with non-functioning adenomas. Moreover, mortality in patients with MACS was increased. Regarding effects of treatment for MACS, the evidence is rather limited, although data do imply that adrenalectomy lowered the risk of comorbid conditions.

Cortisol autonomy might be a biological continuum without clear separation between non-functioning adenomas and functioning adenomas associated with cortisol excess.[1,2,58] In the 2016 ESE-ENSAT guidelines, the term "autonomous cortisol secretion" was introduced for patients with adrenal incidentaloma and cortisol levels after 1mg-DST of >138 nmol/L, with "possible autonomous cortisol secretion" for cortisol levels after 1mg-DST between 50 and 138 nmol/L.[1] One main message of this systematic review is that patients with possible autonomous cortisol have a similar prevalence of comorbidities potentially attributable to cortisol, which is clearly higher than in patients with non-functioning adenomas. Therefore, the new guideline defines MACS by cortisol >1.8 µg/dL post-1mg-DST.[2] Moreover, the present review showed that any cortisol cut-off value post-1mg-DST has an overall poor accuracy to predict prevalent or incident comorbidities. Several studies have reported higher rates of comorbidities with increasing post-1mg-DST cortisol levels, with the relationship being non-linear.[41,42,55,56] However, with the present evidence, a cortisol level cut-off of ≤50 nmol/L (≤1.8 µg/dL) following 1mg-DST appears to discern patients at risk for suffering from comorbidity-related clinically relevant cortisol overproduction. In the future, the additional relevance of ACTH suppression on MACS-associated comorbidities should be investigated. Notably, the 1mg-DST—as all assays using a cut-off level—is subject to misclassifications based on inter- and intra-assay variations and biological variations. To further assess the robustness of the cut-off level including their validity when used for treatment decisions, individual patient data (IPD) analysis is warranted.

Overall, there is an increasing body of evidence on an association between MACS and hyperglycemia and hypertension, as evidenced by this review[11,19-63] and other studies.[23,75-82] However, measurement methods were variable, imprecise (eg, manual BP measurement using arm cuffs (ie, sphygmomanometer)), and often not described in detail, which might result in missing subtle, clinically relevant BP abnormalities (eg, lack of night dipping).[83] The association with dyslipidemia is less solid, although biologically plausible.[26,28-36,38,39,41-44,47,50,54,55,58,64] We would like to emphasize key warnings for the interpretation of the aforementioned results: (1) the accuracy of the 1mg-DST has not been validated, which may result in false-positive and false-negative results, (2) all reported studies based on retrospective analyses may be prone to selective reporting of endpoints, and (3) no study has provided comparisons of patients with MACS to a matched reference cohort of patients without

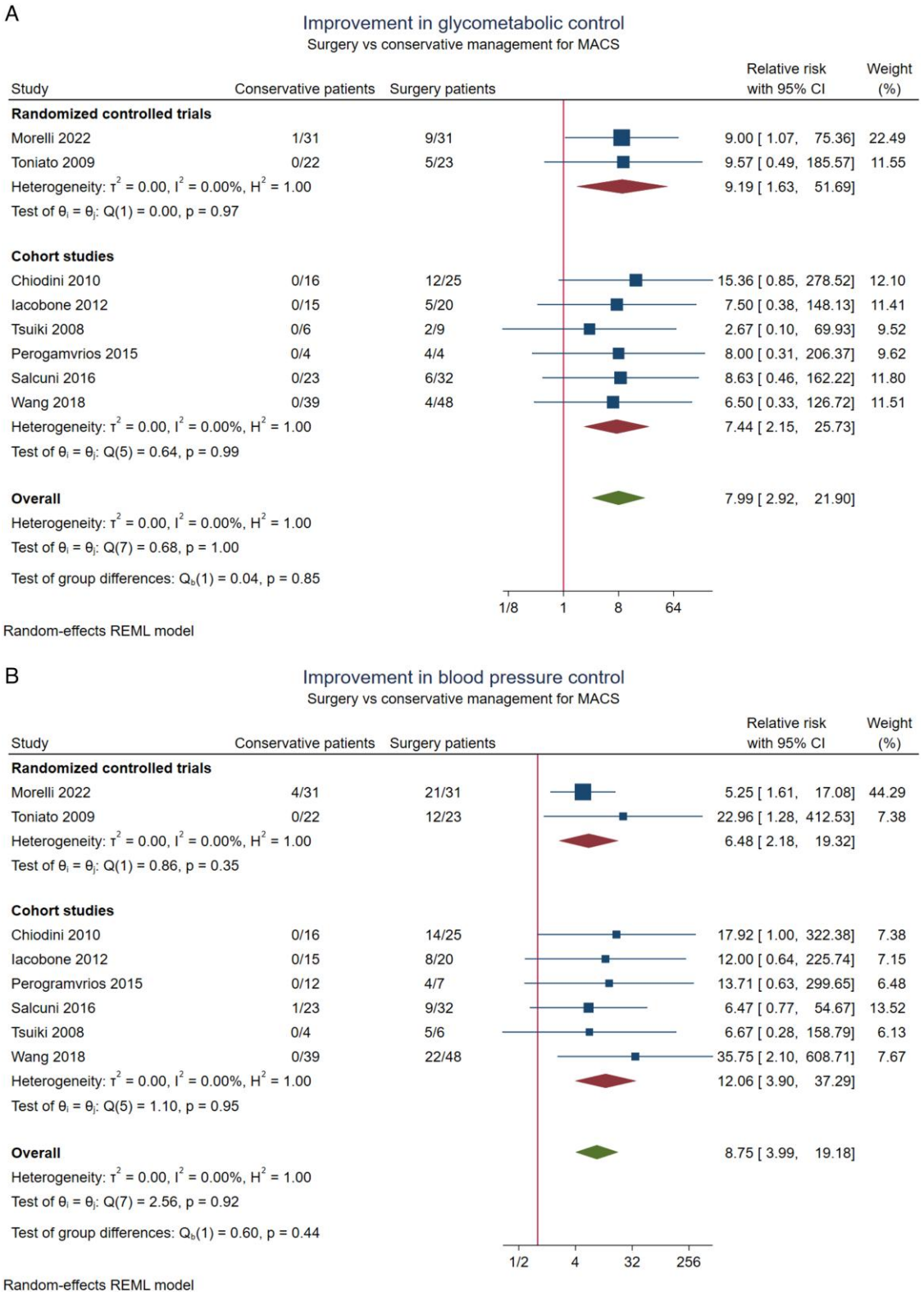

Figure 6. Summary of RR for improvement in glucometabolic and cardiovascular parameters in patients with adrenal incidentaloma and MACS following treatment. RR with CIs for the improvement in (A) glucometabolic control, (B) hypertension, and (C) dyslipidemia as reported were included in the random-effects maximum likelihood (REML) meta-analysis based on the different cut-offs for MACS following the 1mg-DST. The squares and horizontal lines correspond to the RR with 95% CIs. The upper two diamonds represent the pooled HR and 95% CI for the RCT and cohort studies, respectively. The lowest diamond represents the pooled HR and 95% CI combining the RCT and cohort studies. The reference line represents the estimate of 1.0 meaning no difference between the patient groups. MACS, mild autonomous cortisol secretion.

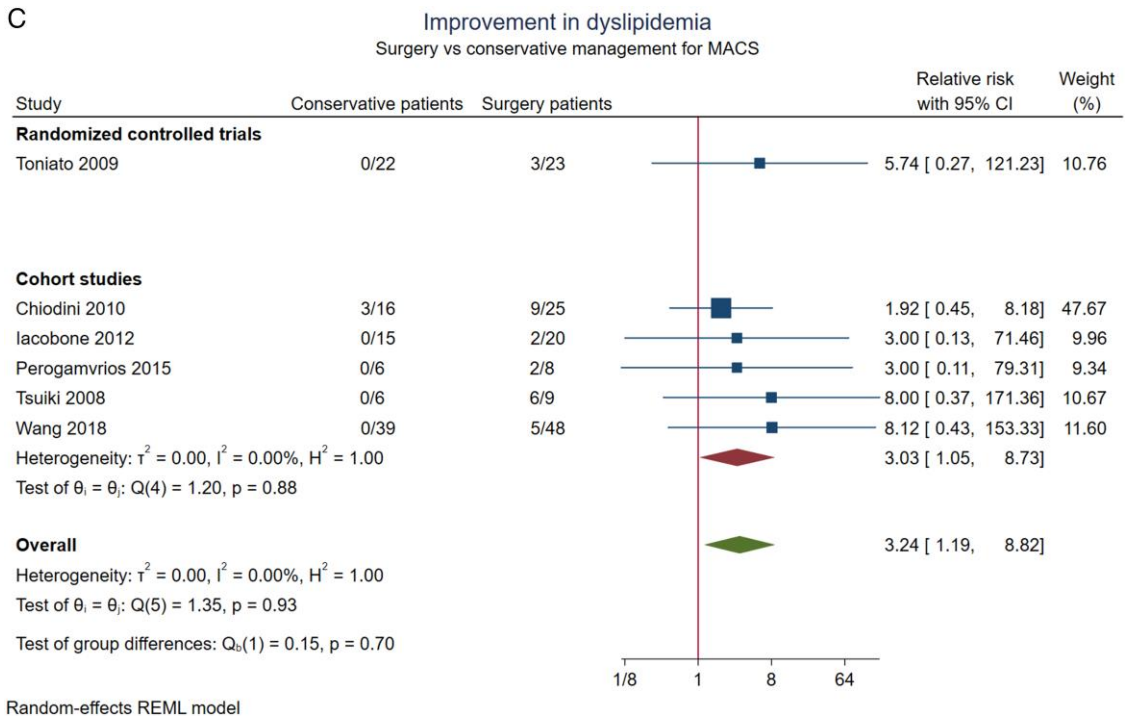

Figure 6. Continued

adrenal incidentaloma. This comparison is necessary to judge the true impact of the adrenal tumor on the different comorbidities, since certain diseases (eg, diabetes) might increase the risk for adrenal tumors (and not solely vice versa).[79] Nevertheless, this review highlighted that MACS is associated with negative cardiovascular risk profiles, including evidence for an association between MACS and an increased risk of cardiovascular events and excess mortality.

Since observational studies—by design—cannot prove causality, interventional studies are of key importance. This review suggests that surgery may improve the cardiovascular risk profile, although evidence is weak. As only 475 patients (including 54 randomized patients) treated with surgery were compared to controls and as the different studies included a heterogeneous group of patients, it is currently not possible to define exact indications for surgery for patients with MACS.[60,64-73] In addition to the limitations mentioned above, none of the published studies evaluated the endpoints in a standardized manner, and medical treatment was not standardized, which is of importance to compare and interpret the effect of therapeutic interventions. Importantly, no data were available on more clinically relevant endpoints (eg, mortality or major cardiovascular events) following surgery or other treatment strategies. Moreover, post-abdominal surgery weight loss might influence the cardiovascular risk profile, leading to non-hormonal effects influencing the study outcome. In the included RCTs comparing adrenalectomy to conservative management for MACS, the influence of post-abdominal (adrenal) surgery weight loss on the reported outcomes is not a general rule, as—surprisingly—50% and 76% of patients, respectively, did not lose weight post-surgery.[65,66] Future studies should focus on the indications of adrenalectomy in patients with MACS.

The present systematic review and meta-analysis were part of the recent update to the clinical guideline on adrenal incidentalomas[1,2] and highlight the clinical importance of the condition MACS. In conclusion, MACS is associated with an increased risk for multiple metabolic or cardiovascular comorbidities and mortality. Moreover, adrenalectomy of the adrenal adenoma causing MACS appeared to be beneficial. Due to the limited sample size, the heterogeneous definitions of outcome measurements, selective reporting, and significant proportions of missing data, the reported pooled estimates need to be interpreted with caution. In general, the quality of the evidence was low, hampering making strong conclusive remarks and highlighting the need for future prospective studies.

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Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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