Dear Editors and Reviewers,
We would like to thank you for your time and effort reviewing the enclosed manuscript. We appreciate the opportunity to improve the manuscript and provide a point by point response to comments below.

Sincerely, Irina Bancos

Referee: 1

Bancos et al present data from a systematic review and meta-analysis to determine the effect of adrenalectomy compared to conservative management on CV risk factors in patients with SCS and to compare the effect of adrenalectomy on CV risk factors in SCS versus those with non functioning adrenal tumours. The study is carried out well. Very little prospective randomised controlled studies are available and data on this topic have been conflicting. A similar study has been carried out but fewer studies were analysed. The manuscript presents a detailed analysis and gives a comprehensive assessment of all important relevant studies. Limitations are acknowledged.

We thank the reviewer for the nice comment.

1. **Is it possible to assess whether the size of the tumours in patients treated conservatively or surgically predicts an improvement in cardiovascular outcomes?**

   Unfortunately, tumor size was reported inconsistently in the studies and, especially, in the subgroups of studied patients. The originally intended analysis of tumor size versus cardiovascular outcomes was not possible to perform. In the revised manuscript, we added a sentence to the discussion to comment on this important issue.

2. **From the full analysis are data available on whether age and sex determine an improvement in cardiovascular outcomes?**

   Again, both age and gender were inconsistently reported in the studies, making it impossible to perform such an analysis. In the revised manuscript, we added a sentence to the discussion to comment on this important issue.

3. **What was the length of follow up in each study described? This is crucial as may impact results. What did the authors do to compensate for the discrepancy between studies?**

   We agree that heterogeneous times of assessment in relation to surgery may have influenced the results. Table 3 includes the information on time of assessment (column 2) to illustrate this heterogeneity. We accounted for this variability in the assessment of the quality of studies and quality of evidence, however, we did not exclude studies based on this variable. As illustrated in table 3, the majority of studies had a minimum follow up of 6 months. We have now added the following information to the manuscript:
Most studies reassessed patients at least 6 months after the surgery (n=17, Table 3) with a median follow up of 28 (1-109) months (median and mean follow up was reported only in 11 studies).

4. Are data available on what sort of conservative treatment was administered to patients and how cv risk factor treatments changed post operatively?

Very little to no information is provided on “conservative” follow up leading to incertitude on how aggressive the therapy for hypertension, diabetes, etc was in the non-surgical group. The question on whether an intensive therapy for cardiovascular comorbidities may avoid cardiovascular morbidity and mortality remain to be answered in a future, well designed prospective, randomized trial. However, our opinion is that non-surgical populations included in current review reflect the reality of current practice and care of patients with SCS.

5. What dexamethasone cortisol cut-off is associated with best CV outcome post surgically? Can this be deduced from the meta-analysis?

Unfortunately, this cannot be deduced from the current work. As illustrated in the subgroup analysis, similar improvements in hypertension and diabetes have been observed regardless of the cutoff. In the revised manuscript, we added a sentence to the discussion to comment on this important issue.

Referee: 2

The meta-analysis deals with the difficult task of the outcome of adrenalectomy in patients with Subclinical Cushing Syndrome. Although the low to moderate quality and the limited number of study, some results are of interest. However, some concerns derive from reading the manuscript.

1. Page 4, line 93. The Authors included published studies that enrolled at least only 5 operated patients to expand the number of available data. It should be of interest a sub analysis of the studies that included at least 10/15 patients to obtain more robust evidence

Unfortunately, excluding studies with a smaller number of patients will lead to very unstable analysis (since the number of studies was not that large to start with).

2. Page 6, line 135. I suggest to exclude the studies that did not report any cortisol cut-off after 1 mg-DST or the SCS definition, since the aim was to assess the influence of the cortisol secretion on the benefit of adrenalectomy.

Indeed, several studies have not provided either cortisol cutoff after Dexamethasone OR no definition at all. Rather than excluding the studies completely, we performed a subgroup analysis (sup Figure 1 and 2) illustrating no differences in response. Our reason for that was that there is no single clearly defined and acceptable definition of SCS, and while authors have not explained how they defined SCS, patients were clearly diagnosed to have one.
3. The major limit of the available data is that almost 65% of the studies reassessed the patients only few months after surgery. In the paragraphs where the clinical outcome has been reported (in particular for BP or DM) the median follow-up of the selected studies should be added.

We agree that heterogeneous times of assessment in relation to surgery may have influenced the results. Unfortunately, 7/25 studies provided no information on the timing of the follow up. However, the majority assessed patients at least 6 months after surgery. In the revised manuscript, we added the median follow up for studies to the result section. We have now added the following information to the manuscript:

*Most studies reassessed patients at least 6 months after the surgery (n=17, Table 3) with a median follow up of 28 (1-109) months (median and mean follow up was reported only in 11 studies).*

4. Page 13, line 294. In the Conclusions a note of caution should be added limiting the consideration of the beneficial effects of adrenalectomy to the short follow-up reported by the majority of the studies.

We agree. In the revised manuscript, we added a sentence to the conclusion emphasizing that inference should be limited to a follow up of at least 6 months across the included studies.