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# Systematic Review and Meta-Analysis of the Metabolic Effects of Modified-Release Hydrocortisone versus Standard Glucocorticoid Replacement Therapy in Adults with Adrenal Insufficiency

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## **Abstract**

**Context:** Published studies exploring the metabolic effects of Modified-Release Hydrocortisone (MR-HC) replacement in patients with adrenal insufficiency (AI).

**Objective:** To compare metabolic effects of MR-HC with Standard Glucocorticoid (SG) replacement in adults with AI. Randomised control trials (RCTs) were meta-analysed; non-RCT studies described narratively with critical appraisal.

**Data sources:** PubMed/Medline, EMBASE, CINAHL and CENTRAL were searched to identify relevant articles, published before Aug 2019.

**Study selection:** All study types that reported metabolic profile (including anthropometric, glucose and lipid-related parameters), on patients switched from SG to MR-HC replacement. Following independent screening from two reviewers, 390 studies were identified, of which 9 studies were included for review (RCT, n=2; non-RCT, n=7).

**Data extraction:** Two independent reviewers assessed each paper for bias and data extraction.

**Results:** Meta-analysis from RCTs (n=2), 104 patients were switched from SG to MR-HC replacement. Combining treatment effects, at 3-months post-therapy switch there was significant reduction in body weight (-0.82kg; 95% CI: -1.24kg to -0.40kg; p<0.001) and HbA1c (-0.13%; 95% CI: -0.214% to -0.045%; p=0.003). In the sub-group with Diabetes Mellitus (DM), reduction in HbA1C was more pronounced (-0.52%; 95% CI: -0.82% to -0.23%; p<0.001). Non-RCT studies showed improved anthropometric measures and glucose metabolism up to 48-months following switch from SG to MR-HC replacement.

**Conclusions:** In adults with AI, replacement with MR-HC associates with significant improvements in anthropometric measurements and HbA1c compared with SG replacement, particularly those with DM.

## Introduction

Effective management of adrenal insufficiency (AI), regardless of underlying aetiology, usually requires lifelong glucocorticoid replacement therapy<sup>1, 2</sup>. Ideally, glucocorticoid replacement regimes should mimic physiological diurnal patterns of plasma cortisol, with an early morning peak and mid-night trough<sup>3</sup>. Steroid replacement lowers overall risk of life-threatening adrenal crisis<sup>4</sup>, a condition which previously had a 100% mortality rate prior to administration of pharmacological glucocorticoid replacement therapies<sup>5,6</sup>. Unfortunately however, despite overall improvements in mortality, administration of steroid replacement therapies in patients with AI still associates with an increased mortality rate<sup>7,8</sup>, metabolic dysfunction (including weight-gain and impaired glucose metabolism<sup>9</sup>) and immune dysfunction (including impairment of natural-killer cell function<sup>10</sup>).

The underlying aetiology of the associated increased mortality and metabolic and associated with glucocorticoid replacement in AI remains incompletely understood and contentious. Possible mechanisms include chronic exposure to excessive glucocorticoid action, and mismatch between plasma profiles associated with exogenous steroid replacement and those reflective of physiological circadian rhythm of endogenous glucocorticoid<sup>11</sup>. Data drawn from retrospective studies have suggested that increased morbidity and mortality could result from higher doses previously administered to AI patients, and the importance of tailoring regimes to patients with more emphasis on timing of intake<sup>12</sup>.

Hydrocortisone (usually administered orally, three times per day) is used most commonly for steroid replacement in adults with AI both in the UK<sup>13</sup>, and worldwide<sup>14</sup>. Modified-Release Hydrocortisone, (MR-HC, brand name *Plenadren*, administered orally just once per day), used in <2% of patients in the UK currently<sup>13</sup>, has delayed absorption from the gut. Plasma cortisol levels with exogenous MR-HC in AI demonstrate superior replication of the normal physiological diurnal and circadian rhythm of endogenous cortisol (in subjects with an intact hypothalamo-pituitary adrenal axis), compared with thrice-daily standard hydrocortisone replacement<sup>15</sup>. MR-HC replacement regimes however still fail to replicate the physiological nocturnal rise in cortisol, the clinical importance of which is still not known<sup>11</sup>.

Replacement with MR-HC in patients with AI may restore expression of clock genes regulated by the normal physiological circadian rhythm of endogenous cortisol<sup>16</sup>. Furthermore, MR-HC has been shown to improve metabolic profile including anthropometric measures and glucose handling<sup>15,17</sup>.

Despite the evidence outlined here showing the benefits of MR-HC in patients with AI, regarding metabolic profile, there are relatively few reported studies that compare directly the metabolic effects of MR-HC versus Standard Glucocorticoid (SG) replacement in patients with AI. Our objective, was to perform the first meta-analysis of these studies alongside a formal systematic review of the metabolic effects of MR-HC versus SG replacement in adult patients with AI.

## **Methods and Materials**

**Search Strategy:** Systematic literature search performed on all articles published until July 2019, using the online databases: Medline/PubMed; EMBASE; CINAHL, and; CENTRAL. (Search strategies detailed in *supplementary appendix*). Keywords used in search strategies: (Adrenal Insufficiency OR Addison’s OR Hypopituitarism OR [“Adrenal” AND “Insufficiency”] OR “Addison” OR “Hypopituitarism”) AND (Glucocorticoids OR Hydrocortisone OR Cortisone OR Prednisolone OR “Glucocorticoids” OR “Hydrocortisone” OR “Cortisone” OR “Prednisolone”) AND (Plenadren OR Chronocort OR Delayed Action Preparations OR [“Dual” OR “Modified” OR “Delayed” OR “Sustained”] AND “Release”). There were no restrictions on language or time restrictions. Search outputs were imported into Covidence<sup>18</sup>.

**Inclusion Criteria:** For all identified papers, titles and abstracts were screened by two independent reviewers (CB and PH), to identify relevance. For those abstracts that included metabolic outcome measures in patients with AI treated with MR-HC, these articles proceeded to full text review. Following full text review, articles were included in the review if they satisfied four key inclusion criteria (*table 1*):

- 1) Publication in peer-reviewed journal;
- 2) Subjects aged 18 years or older;
- 3) Any type of AI, switched from SG to MR-HC replacement;
- 4) Metabolic outcome measures (anthropometric, glucose and lipid metabolism).

**Exclusion Criteria:** We excluded any studies reporting on glucocorticoid usage for *non*-endocrine conditions, and endocrine conditions other than AI.

Our initial search revealed 390 abstracts, of which we eliminated 86 due to duplication. Of the 304 remaining articles, 295 were excluded (*figure 1*). Following application of inclusion and exclusion criteria, we included 9 relevant articles in our review.

**Data Extraction:** Data extraction consisted of a tabular summary of number of participants, duration of follow up, outcome measurements and corresponding quality assessments (*table 2*). Primary outcomes included anthropometric measures (BMI and bodyweight) and glucose metabolism (change in HbA1c) in all patients. Secondary outcomes included serum lipids, and sub-group analyses on glycaemic changes in those patients with both AI and diabetes mellitus (DM). Units are reported for HbA1c as percentage glycosylated haemoglobin (%), as not all studies reported in SI unit of mmol/mol. For serum lipids units are reported as mg/dL for consistency as the vast majority of studies reported in these units, and those studies that did not were converted to mg/dL.

We present data from non-RCT studies (mean and standard error, median and range and standard error where possible) in summary tables, with p-values for statistical hypothesis testing. We contacted study authors for any missing data. Where missing data were not available from the study author, attempts were made to obtain approximations from digitising published graphs<sup>19</sup>.

**Quality Assessment of Studies:** The quality of randomised controls was assessed using the Cochrane collaboration tool<sup>20</sup>, with the revised tool used for randomised cross-over trials<sup>21</sup>. The Newcastle Ottawa Scale was used for non-randomised studies<sup>22</sup>: a maximum score of 9 could be assigned for each study, with a score of >6 considered to be of high quality. Single-arm studies were quality-assessed using an adapted tool with 4 main criteria: selection; ascertainment; causality, and; reporting<sup>23</sup>. For these studies, an assessment for each domain was made, followed by judgement of overall quality<sup>23</sup>.

**Statistical Analysis:** We applied meta-analysis on data from RCTs (with 95% confidence intervals [95% CI]) to calculate overall treatment effect size, using fixed-effects or random-effects model. We calculated 95% CI from sample size and standard deviation for those studies only reporting standard deviations. For variables with insufficient data reported, we contacted authors of the original studies, and utilized any additional data supplied. Between-study heterogeneity was assessed using I-squared, with a p-value of >0.10 set as a threshold for application of fixed-effects model, and a p-value  $\leq$ 0.10 for application of random-effects model, where possible. A p-value of <0.05 was considered statistically significant for individual tests.

Regarding assessment of primary outcomes of changes in bodyweight, BMI and HbA1c in all patients, a Bonferroni corrected p-value of 0.0167 was set to preserve the overall type 1 error rate at 0.05. Secondary outcomes and additional analysis of HbA1c change in DM were considered significant with an unadjusted p-value of <0.05. We did not perform any formal

tests for sensitivity analysis and publication bias due to insufficient data. We used a narrative synthesis for non-RCT (including single-arm) studies.

## Results

**Study Characteristics:** The initial literature searches retrieved 390 papers, with 9 papers meeting the inclusion criteria to proceed to this systematic review<sup>15,17,24-30</sup>. Just two trials meet criteria for inclusion in RCT meta-analysis<sup>15,17</sup> (*table 2*). One RCT was a cross over trial with 60 participants from Sweden, all of whom had a confirmed diagnosis of primary AI. This study compared the metabolic effects of MR-HC with standard hydrocortisone replacement (administered three times per day), with data up to 3-months<sup>15</sup>. The other RCT was a parallel design from Italy with inclusion of patients with a confirmed diagnosis of either primary or secondary AI. This study included patients on MR-HC (n=46) and SG therapy (n=43). SG therapies included orally administered hydrocortisone or cortisone (administered either twice or thrice daily), with data up to 6-months<sup>17</sup>.

Non-RCT studies included one prospective study from Germany with patients confirmed to have either primary or secondary AI, including those opting to switch to MR-HC (n=30), and those remaining on standard hydrocortisone (n=20) and followed up between 3 and 9 months<sup>25</sup>. A further non-RCT was a retrospective cohort study from Italy with patients switched to MR-HC (n=53) and those remaining on standard hydrocortisone (n=47), with metabolic outcomes compared at baseline up to 48-months<sup>30</sup>.

The single-arm studies all took place in Italy, with three prospective studies<sup>24,27,28</sup> and two retrospective studies<sup>26,29</sup>. The single-arm prospective studies each included 19 participants. One prospective study consisted only of patients with primary AI treated with MR-HC for 12-months<sup>28</sup>. The other two prospective studies consisted of patients with a mixture of primary and secondary AI, treated with MR-HC for a duration of between 6 and 12 months<sup>24,27</sup>. The two retrospective studies included between 14 and 49 patients, with follow up ranging between 24 and 36 months<sup>26,29</sup>.

**Risk of Bias in RCTs:** The parallel RCT reported by Isidori and colleagues<sup>17</sup> was assessed using the Cochrane risk of bias tool<sup>20</sup> (see *appendix*). The study had a low risk of bias in all categories except blinding of participants: recruited patients were aware of their steroid

replacement (switch to once daily MR-HC or continued SG regime). The study authors outlined negative experience of prior trials that adopted a double-blind design for patients with AI<sup>17</sup>.

The randomised cross-over RCT reported by Johannsson and colleagues<sup>15</sup> was assessed using a revised tool for crossover trials<sup>21</sup>. There is some risk of bias in this study due to its open design, with no blinding of either participants or outcome assessors. The authors justify this design though, based on safety implications of adrenal crisis in a blinded patient randomized to placebo requiring doubling of dose<sup>15</sup>. The ongoing and continuous need for steroid replacement therapy in patients with AI meant it was not possible to include a 'wash out' period<sup>15</sup>. Lack of reported method of randomisation and allocation concealment may have contributed to bias risk, but there was low risk for all other categories explored.

**Meta-Analysis of RCTs:** The two RCTs both provide data up to 3-months following switch to MR-HC<sup>15,17</sup>. Isidori and colleagues<sup>17</sup> presented data as treatment effect difference between SG and switched MR-HC treatment groups in an ANCOVA analysis adjusted for age, subtype of AI, DM and smoking status. Data from the crossover trial reported by Johannsson and colleagues<sup>15</sup> presented data as treatment difference, calculated from within-individual comparison of SG and MR-HC treatments. Johannsson et al.<sup>15</sup> provided additional standard deviation data for treatment differences between groups. The cross-over trial was included in our meta-analysis since the authors reported treatment effect calculated from within-individual comparison of treatments<sup>31</sup>. Isidori et al. provided unpublished data of glucose metabolism in patients with DM and subsequent treatment effect (*raw data for meta-analyses supplied in appendix*).

Meta-analysis of combined data from the two RCTs outlined (with crossover and parallel design), showed significant reduction in BMI and body weight in adult patients with AI switched from SG to MR-HC at 3-months (BMI  $-0.27\text{kg/m}^2$  [95% CI:  $-0.41$  to  $-0.13$ ];  $p < 0.001$ ; body weight  $-0.82\text{kg}$  [95% CI:  $-1.24$  to  $-0.40$ ];  $p < 0.001$ ). There was no significant between-study heterogeneity for either BMI ( $I^2 = 33.2\%$ ,  $P_{\text{heterogeneity}} = 0.221$ , *figure 2A*) or body weight ( $I^2 = 0\%$ ,  $P_{\text{heterogeneity}} = 0.352$ , *figure 2B*). Meta-analysis of glucose metabolism showed a significant reduction in HbA1c in all patients at 3-months following switch from SG to MR-HC replacement (HbA1c  $-0.13\%$  [95% CI:  $-0.21$  to  $-0.04$ ];  $p = 0.003$ ), with no significant between study heterogeneity ( $I^2 = 0\%$ ,  $P_{\text{heterogeneity}} = 0.643$ , *figure 2C*). A separate meta-analysis of HbA1c change at 3-months in those patients with DM showed a greater reduction in HbA1c ( $-0.52\%$  [95% CI:  $-0.81$  to  $-0.23$ ];  $p < 0.001$ ), with no evidence of between study heterogeneity ( $I^2 = 0\%$ ,  $P_{\text{heterogeneity}} = 0.505$ , *figure 2D*). The study by Isidori and colleagues also reported on metabolic treatment effects of MR-HC at 6-months following switch from SG replacement



therapy<sup>17</sup>. The effect sizes at 6-months showed significant reduction in BMI (-1.7kg/m<sup>2</sup> [95% CI: -3.0 to -0.5]; p=0.008); body weight (-4kg [95% CI: -6.9 to -1.1]; p=0.008) and HbA1c (-0.3% [95% CI: -0.5 to -0.1]; p=0.001)<sup>17</sup>. Addition unpublished data provided by Isidori et al., showed a reduction of HbA1c in DM (-0.78% [95% CI: -1.10 to -0.47]; p=0.002)<sup>17</sup>.

Meta-analysis (fixed effects model) of secondary outcome measures showed no significant change in total cholesterol (-1.34mg/dl; [95% CI: -5.34 to 2.67]; p=0.513, *figure 3A*). As there was some evidence of between study heterogeneity ( $I^2=70.7\%$ ,  $P_{\text{heterogeneity}}=0.065$ ), a random effects meta-analysis was performed which also showed no significant change in total cholesterol (-4.64 mg/dl; [95% CI -16.08 to 6.82; p=0.428, *figure 3B*). Meta-analysis of separate serum lipids showed significant evidence of change in HDL cholesterol (-4.4mg/dl; [95% CI: -6.38 to -2.42]; p<0.001, *figure 4A*), with no between study heterogeneity ( $I^2=47\%$ ,  $P_{\text{heterogeneity}}=0.169$ ). Meta-analysis of LDL cholesterol showed no significant change (-0.197mg/dl; [95%CI -3.26 to 2.88]; p=0.900, *figure 4B*), with no significant between study heterogeneity ( $I^2=0$ ,  $P_{\text{heterogeneity}}=0.636$ ). Triglycerides showed evidence of change at 3-months (6.98 mg/dl; [95% CI: 0.781 to 13.188]; p=0.027, *figure 4C*), with no evidence of between study heterogeneity ( $I^2=4.5\%$ ,  $P_{\text{heterogeneity}}=0.306$ ). Meta-analysis of six-month data provided by Isidori et al. followed a similar pattern, with significant change in HDL cholesterol (-9mg/dl; [95% CI: -15 to -3]; p=0.002). There no significant changes in total cholesterol (0mg/dl; [95% CI: -16 to 15]; p=0.962), LDL cholesterol (7mg/dl; [95% CI: -8 to 21]; p=0.364) and triglycerides (7mg/dl; [95% CI: -35 to 21]; p=0.605)<sup>17</sup>.

**Bias Assessment of Non-RCTs:** The Newcastle-Ottawa scale (NOS) used for cohort studies was used for assessing the risk of bias assessment of the non-RCTs<sup>22</sup> (see *appendix*). Quinkler and colleagues reported a prospective study in which patients chose to either switch to MR-HC or remain on their SG replacement therapy, thereby causing a selection bias.<sup>25</sup> In the group that switched to MR-HC replacement, 6 had received (once-daily) prednisolone as their SG replacement regime prior to recruitment. None of the patients who opted to remain on SG therapy had previously had exposure to prednisolone therapy. Patients were followed up whenever their next clinic appointment was, causing a wide range of follow up time: patients switched to MR-HC had a median follow up time of 128 days (range 68-429 days); those who remained on SG therapy had a median follow up time of 338 days (range 98-498 days). The differences in both follow up time and prior SG replacements between groups introduces a risk of bias in comparability. Overall, the study reported by Quinkler and colleagues,<sup>25</sup> scored 5 on NOS scale indicating concerns of bias.

The retrospective study reported by Guarnotta et al. (A)<sup>30</sup> analysed patients referred to Palermo University between 2008 and 2013. There were baseline differences in

characteristics between the cohorts (including those switched to MR-HC of higher BMI and metabolic risk). Overall, the study reported by Guarnotta et al. (A)<sup>30</sup> scored 6 on NOS scale indicating concerns of risk of bias.

**Narrative Synthesis of Non-RCTs:** The prospective study reported by Quinkler et al.<sup>25</sup> showed significant reductions of BMI ( $p=0.003$ ) and HbA1c ( $p=0.014$ ) for patients switched from SG to MR-HC, with the retrospective study by Guarnotta et al. (A)<sup>30</sup> also showing significant reductions in BMI ( $p=0.002$ ) and HbA1c ( $p<0.001$ ) for patients switched from SG to MR-HC (data in *table 3*). Neither study reported body weight as an outcome. The control group remaining on SG (oral hydrocortisone) in the study by Quinkler et al.<sup>25</sup> showed no significant changes across primary outcomes. However, over 48-months the control group on SG replacement in study by Guarnotta et al. (A)<sup>30</sup> showed significant increases in BMI ( $p<0.001$ ) and HbA1c ( $p<0.020$ ).

Regarding secondary outcomes, Quinkler et al.<sup>25</sup> showed a significant decrease in total cholesterol ( $p=0.016$ ) in the group switched to MR-HC, but no change in the control SG group ( $p=0.332$ ). There were no significant changes in other serum lipids across the 'switch to MR-HC' and control SG groups. The study by Guarnotta et al. (A)<sup>30</sup> showed significant decreases in total cholesterol ( $p=0.006$ ) and LDL cholesterol ( $p=0.005$ ) at 48-months in the group switched to MR-HC therapy, and significant increases in LDL cholesterol ( $p=0.018$ ) in the SG control group. There were no significant changes in HDL cholesterol or triglycerides in either group.

**Bias Assessment of Single-Arm Studies:** There were 3 prospective single-arm studies<sup>24,27,28</sup> and 2 retrospective studies<sup>26,29</sup>, varying in size from 14 to 49 participants. The study reported by Giordano et al.<sup>28</sup> recruited 19 patients with primary AI, at a single centre in Italy, deemed low risk for bias across all domains (risk of bias table in *supplementary appendix*). Ceccato et al.<sup>24</sup> recruited 19 patients with either primary or secondary AI with some risk of bias for causality due to a wide range of follow up time. The retrospective study by Frara et al.<sup>26</sup> included 14 patients with secondary AI, and a focus on bone density and reporting bias related to metabolic measurements due to missing data. Guarnotta et al (B)<sup>29</sup> recruited 49 patients and presented results separately for pre-diabetic and normal glucose tolerance patients and was considered low risk across all domains. The prospective study reported by Mongioi et al.<sup>27</sup> had high risk of bias for ascertainment and causality. Some patients in this reported study were treatment naïve with recent diagnosis of AI.<sup>27</sup>

**Narrative Synthesis of Single-Arm Studies:** (Results for all single-arm studies are summarised in *table 4*). For primary outcomes, the largest study with 49 patients reported by Guarnotta et al. (B)<sup>29</sup> showed a significant reduction in BMI after 36-months following switch to MR-HC compared to the group who remained on SG therapy. None of the other reported studies<sup>24,26-28</sup> showed any significant changes in BMI. The studies reported by Guarnotta et al. (B)<sup>29</sup> and Giordano et al.<sup>28</sup> reported significant reductions in HbA1c at their final endpoints of 36-months and 12-months respectively following switch to MR-HC. Patients with primary AI but not secondary AI had significant improvement in HbA1c following switch to MR-HC in the study reported by Mongioi et al.<sup>27</sup>. There were no reports of any significant changes in HbA1c in the other studies<sup>24,26</sup>. The only paper to report on body weight was by Giordano et al.<sup>28</sup>, which showed no significant changes.

For secondary outcomes, the studies by Ceccato et al.<sup>24</sup> and Giordano et al.<sup>28</sup> showed significant decreases in total cholesterol following switch to MR-HC. There was a significant decrease in LDL cholesterol in the study reported by Giordano et al.<sup>28</sup>. In the study reported by Guarnotta et al. (B)<sup>29</sup> there was a significant decrease in HDL cholesterol following switch to MR-HC. There were no significant changes in any other serum lipids measurements across studies<sup>24,26-29</sup>.

## Discussion:

This systematic review and meta-analysis of 2 randomised studies <sup>15,17</sup> showed significant improvement in all metabolic primary outcomes at 3 months after switching to MR-HC. There were additional improvements in glucose metabolism in patients with concomitant diabetes <sup>15,17</sup>. Two non-randomised studies <sup>25,30</sup> and 5 single-arm studies <sup>24,26-29</sup> supported these findings with the higher quality and larger sample size studies showing improved anthropometric measures and glucose metabolism up to 48 months post switching to MR-HC.

Both randomised trials <sup>15,17</sup> showed significant improvement across all primary outcomes, with the meta-analysis being primarily weighted by the crossover study, due to its smaller confidence intervals. This would be expected in the crossover study <sup>15</sup> as patients act as their own controls, and there is large individual variation in response to steroids in AI patients <sup>15</sup>. Additionally the cross-over trial<sup>15</sup> used only thrice-daily hydrocortisone in the control group and only primary AI patients, compared to hydrocortisone or cortisone as the control group and all types of AI in the RCT<sup>17</sup>, further contributing to variation in treatment effect size. Sub-group analysis was not performed due to the small patient number, and analysis for secondary AI patients and patients on different glucocorticoid regimes prior to switch were only available for one study. The ANCOVA treatment effect calculated in the Isidori study<sup>17</sup> did use AI subtype as a covariate to partially account for this in combination with the Johansson study<sup>15</sup> in meta-analysis. Isidori et al<sup>17</sup> used a conversion of 0.8mg hydrocortisone to 1mg cortisone which they stated as being per European Medicines Agency providing some adjustment for the effects of different SG replacement.

The crossover trial was included in meta-analysis, despite its heterogeneity due to the limited number of randomised studies. The cross-over trial <sup>15</sup> is likely to have a carry-over effect as washout is not possible. The limited number of studies available is the main limitation to this analysis and would need repeating when further trials are performed. Whilst the RCT has a degree of carry-over effect as patients are converted from SG replacement to MR-HC, the cross-over trial has the additional carry-over when patients are switched from MR-HC back to hydrocortisone. Carry-over effect creates uncertainty regarding treatment effect <sup>31</sup>. In this case the carry-over possibly risks under-estimate of effect as MR-HC could potentially give long lasting benefit on switching back to hydrocortisone.

The RCT showed additional benefit at 6 months<sup>17</sup>, with the individual paper itself commenting a treatment by time interaction starting at 3 months and improving further at 6 months<sup>17</sup>. Therefore, there is expected to be greater treatment effect beyond the 3-month time point of meta-analysis, and further adequately powered randomised trials are required of longer duration to assess the long term effects of MR-HC on metabolic outcomes.

The non-randomised studies<sup>25,30</sup> agree with the findings of the RCTs, but are both limited by selection bias. In Quinkler et al.<sup>25</sup> patients selected what treatment they wanted with further limitation of patients not having a uniform follow-up time. Guarnotta et al. (A)<sup>30</sup> showed patients being switched to MR-HC being of greater metabolic risk than those remaining on SG therapy. An advantage of this selection bias however, was the degree of improvement shown by high risk patients switched to MR-HC and the progressive metabolic risk shown by patients remaining on SG replacement<sup>30</sup>. The strength of these studies are the large sample sizes. The 48 months follow up time in Guarnotta et al. (A)<sup>30</sup> provides the longest term data on the effects of MR-HC. None of the single-arm studies showed significant change in BMI<sup>24,26-29</sup>, but studies with lower risk of bias paralleled the results of randomised and non-randomised studies with decrease in HbA1c<sup>28,29</sup>.

Across all studies there was a large range in effects observed for secondary outcomes. Meta-analysis showed decrease in HDL cholesterol, and increase in triglycerides at 3 months. Decreased HDL cholesterol persisted at 6 months in RCT<sup>17</sup> but increased triglycerides were not present at 6 months. These findings could convey possible increase in cardio-metabolic risk<sup>32</sup>, although individual studies had not calculated HDL/TC ratios for meta-analysis. Non-randomised studies beyond 6 months show no significant change in HDL cholesterol or triglycerides<sup>25,30</sup>, with evidence of decrease in total cholesterol<sup>25,30</sup>, and additionally in LDL cholesterol up to 48 months<sup>25</sup>. Single-arm studies showed wide variation in effects on cholesterol<sup>24,26-29</sup>.

Prior clinical studies have explored the influence of glucocorticoid replacement regimes on HDL-C levels and cholesterol metabolism. Patients with secondary AI exposed to higher dose glucocorticoid regimes have been shown to have increased HDL-C levels without alteration in triglyceride levels<sup>33</sup>, with an separate study showing that reduced cholesteryl ester transfer protein activity contributes to increased HDL-C levels in high dose glucocorticoid replacement regimes for patients with secondary AI<sup>34</sup>. Glucocorticoid receptor antagonism in patients with Cushing's have been shown to decrease HDL-C levels, but with increased efflux capacity per HDL-C particle<sup>35</sup>. These studies show a complex relationship between

glucocorticoid replacement regimes and HDL-C metabolism. Further studies are needed to explore the effects on HDL-C metabolism and how these changes affect cardiometabolic risk in both MR-HC regimes and SG regimes.

The mechanism for how MR-HC mediates its metabolic improvements is not definitively understood. Equivalent daily dose MR-HC to thrice daily hydrocortisone provides 20% less exposure to glucocorticoids per day<sup>15</sup>, and has been cited as a possible mechanism for the clinical improvements<sup>11,36</sup>. None of the studies performed an adjustment for these pharmacokinetics. The significance of this decreased however is complex in relation to anthropometric measures as an observational study has shown no difference in BMI between high and low doses of hydrocortisone<sup>37</sup>. Decreased exposure to glucocorticoids in AI though have been shown to affect HDL levels in a dose dependent manner<sup>33</sup>. Further clinical studies are needed to definitively assess if the metabolic outcomes from MR-HC are dependent on decreased glucocorticoid exposure, by using a 1.2mg MR-HC to 1mg hydrocortisone ratio or exposure to even higher doses.

Removal of the inappropriate nocturnal exposure to glucocorticoids which occurs in thrice daily hydrocortisone regimes<sup>15</sup>, could however provide the mechanism for the metabolic outcomes of MR-HC. Evening doses of hydrocortisone have been shown to have a more profound hyperglycaemic effect<sup>38</sup>, whilst rodent models have shown that converting from a diurnal regime to same daily dose continuous regime results in development of metabolic syndrome<sup>39</sup>.

An ancillary study of the RCT<sup>17</sup> has shown clock gene expression to be disrupted in AI patients on SG replacement compared to non-AI controls<sup>16</sup>. After switching to MR-HC for 12 weeks disrupted clock gene expression returned to levels of non-AI controls, correlating with the improved metabolic outcomes<sup>16</sup>. More research is needed to further explore the clinical importance of restoring clock gene expression, and how this mediates improved anthropometric measures and glucose metabolism, and its effect on serum lipid levels.

The evidence synthesised in this study showed high quality evidence available up to 6 months, and lower quality evidence up to 48 months. An additional long term study extending from the crossover trial showed no safety concerns over a 5 year period<sup>40</sup>, but had a drop out rate of 7/71 showing a need for further prospective data on long term use of MR-HC and prevention of adrenal crises. Further adequately powered randomised trials over a time periods longer than 6 months are needed for more definitive evidence regarding the long term effects of MR-HC on metabolic outcomes in AI patients with calculated cardiometabolic risk in the form with lipoprotein and apolipoprotein ratios, alongside additional clinical outcomes such as hospital admissions and frequency of adrenal crises.

In conclusion this systematic review shows that from the available evidence to date, MR-HC has superior anthropometric and glucose metabolism compared to SG replacement, particularly for AI patients with concomitant DM. Further work is needed to assess if the changes in serum lipids lead to altered cardiometabolic risk. Additional adequately powered RCTs over a time period of at least 6 months comparing MR-HC to hydrocortisone including additional clinical outcome measures such as frequency of adrenal crisis and cardiovascular risk are required to definitively assess if MR-HC is an optimal form of glucocorticoid replacement. Further work is needed to elucidate the mechanisms by which MR-HC mediates its metabolic improvements and changes to serum lipids, and the clinical significance of better matching the diurnal profile of cortisol in glucocorticoid replacement regimes.

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**PROSPERO Registration:**

PROSPERO                      2018                      CRD42018108509                      Available                      from:  
[http://www.crd.york.ac.uk/PROSPERO/display\\_record.php?ID=CRD42018108509](http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018108509)

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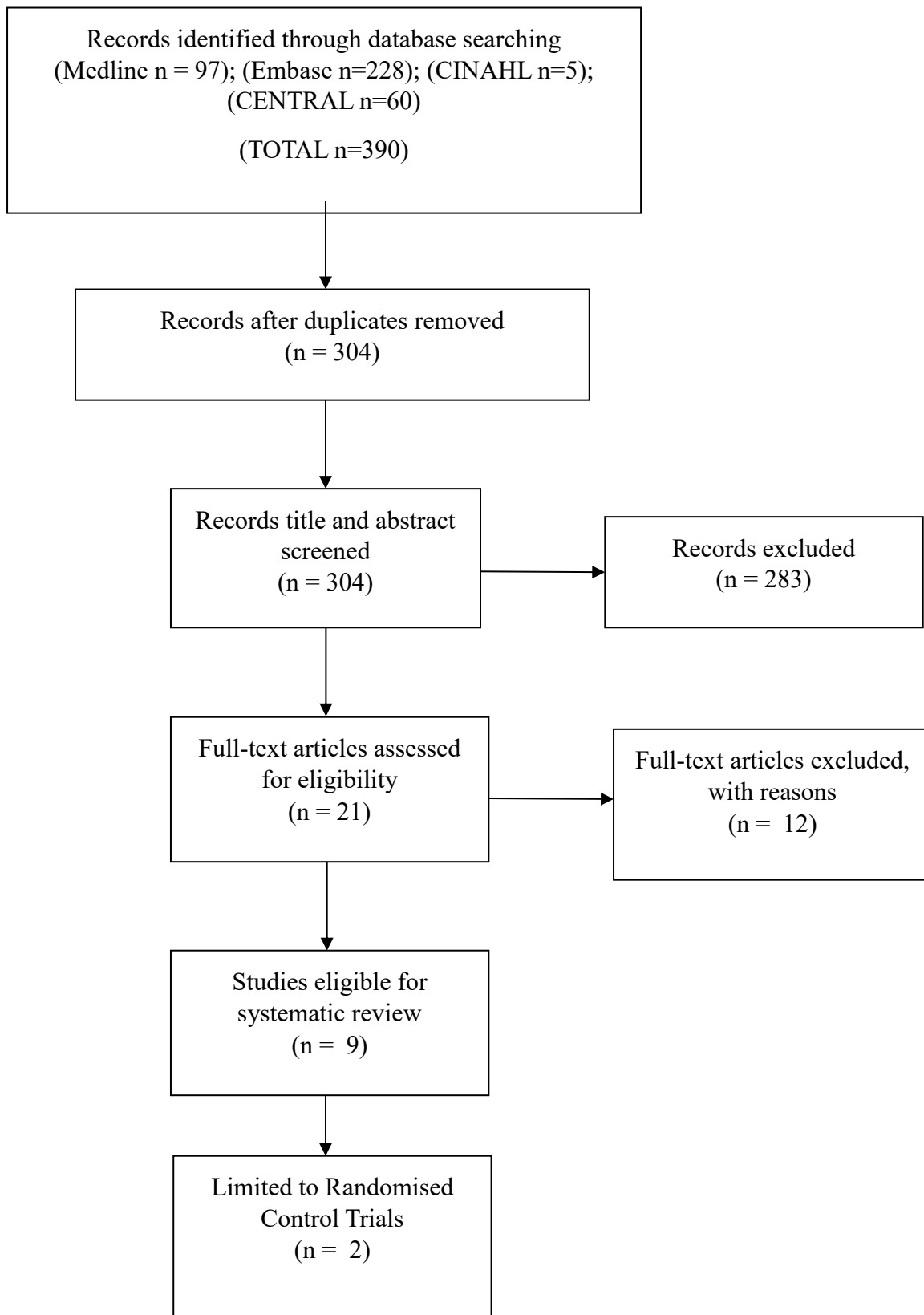
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## Figures and Tables

Table 1: PICOS Criteria for inclusion of studies:

<b>Population</b>	Adult Adrenal Insufficiency Patients
<b>Intervention</b>	Once daily modified release hydrocortisone
<b>Comparator</b>	Standard glucocorticoid replacement
<b>Outcome</b>	Metabolic measurements - primary outcome anthropometric measurement and glucose metabolism; secondary outcome serum lipids
<b>Setting</b>	Primary studies published in peer-reviewed journals;

**Figure 1 - PRISMA Diagram Summarising Literature Search and Selection of Papers**



**Table 2: Main characteristics of Randomised control trials assessing the metabolic effects of modified release hydrocortisone compared to standard glucocorticoid replacement**

<u>First author, year (reference)</u>	<u>Type of Study</u>	<u>Adrenal Insufficiency Types</u>	<u>Follow up Period</u>	<u>Country</u>	<u>Number of Participants</u>	<u>Measurements taken</u>	<u>Summary of Findings with MR-HC Treatment</u>	<u>Summary of Bias Assessment</u>
Johannsson, 2012 <sup>15</sup>	Randomised Crossover Study	Primary	3 months	Sweden	60	Bodyweight; BMI; HbA1c; Serum lipids	Treatment effect: Decreased bodyweight, BMI and Hba1c particularly in patients with diabetes.	Low risk Possible risk of carry-over effect. Patients not blinded to which treatment they receive.
Isidori, 2018 <sup>17</sup>	Randomised Control Trial	Primary and Secondary	6 months	Italy	89 (46 switch treatment, 43 control)	Bodyweight; BMI; HbA1c; Serum lipids	Treatment effect: Decreased bodyweight, BMI and HbA1c.	Low risk Limited by participants not being blinded to treatment.

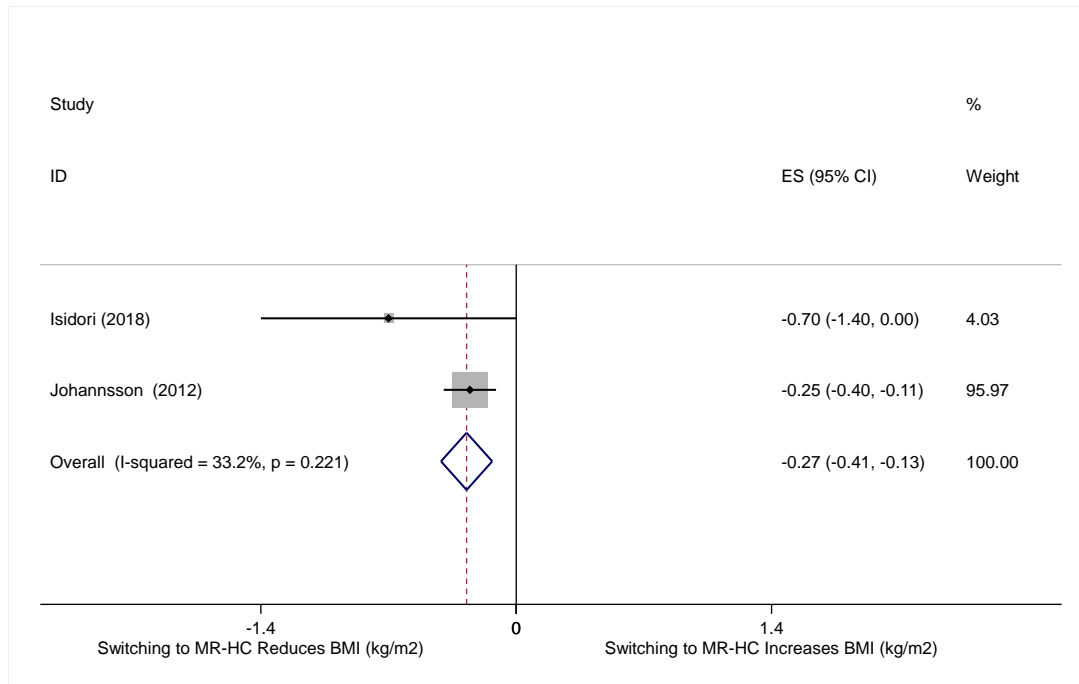
Quinkler, 2015 <sup>25</sup>	Prospective Non-Randomised Control Trial	Primary and Secondary	3-9 months (median 6 months)	Germany	50 (30 switch treatment, 20 control)	BMI; HbA1c; Serum Lipids	Decreased BMI, HbA1c and total cholesterol in switch treatment group. No changes in control group.	Some concerns NOS: 6 Selection Bias as patients selected whether to switch or remain on current treatment. Wide range in follow up time.
Guarnotta, 2019 (A) <sup>30</sup>	Retrospective Cohort Study	Primary and Secondary	48 months	Italy	100 (53 switch treatment, 47 control)	BMI; HbA1c; Serum Lipid	Patients in switch treatment group have decreased BMI; HbA1c and total cholesterol compared to baseline. Control group have increased BMI, HbA1c and total cholesterol	Low risk NOS:7 Patients at baseline in switch treatment group at baseline have significantly elevated HbA1c compared to treatment group.

							compared to baseline.	
Giordano, 2016 <sup>28</sup>	Prospective Uncontrolled Before and After Study	Primary	12 months	Italy	19	BMI; HbA1c; Serum Lipids.	Non-significant decrease in BMI. Progressive decrease in Hba1c after 6 months, particularly in patients with diabetes. Progressive decrease in total and LDL cholesterol.	Low risk across all domains for assessing single arm studies.
Ceccato, 2018 <sup>24</sup>	Prospective Uncontrolled Before and After Study	Primary and Secondary	6-12 months (median 8 months)	Italy	19	Bodyweight; BMI; HbA1c; Cholesterol	Significant decrease in total cholesterol. Non-significant decreases in bodyweight, BMI and HbA1c.	Some Concerns Wide range in follow up time between patients.
Frara, 2018 <sup>26</sup>	Retrospective Case series	Secondary	24 months	Italy	14	BMI; HbA1c; Cholesterol	No significant change in BMI;	Some Concerns

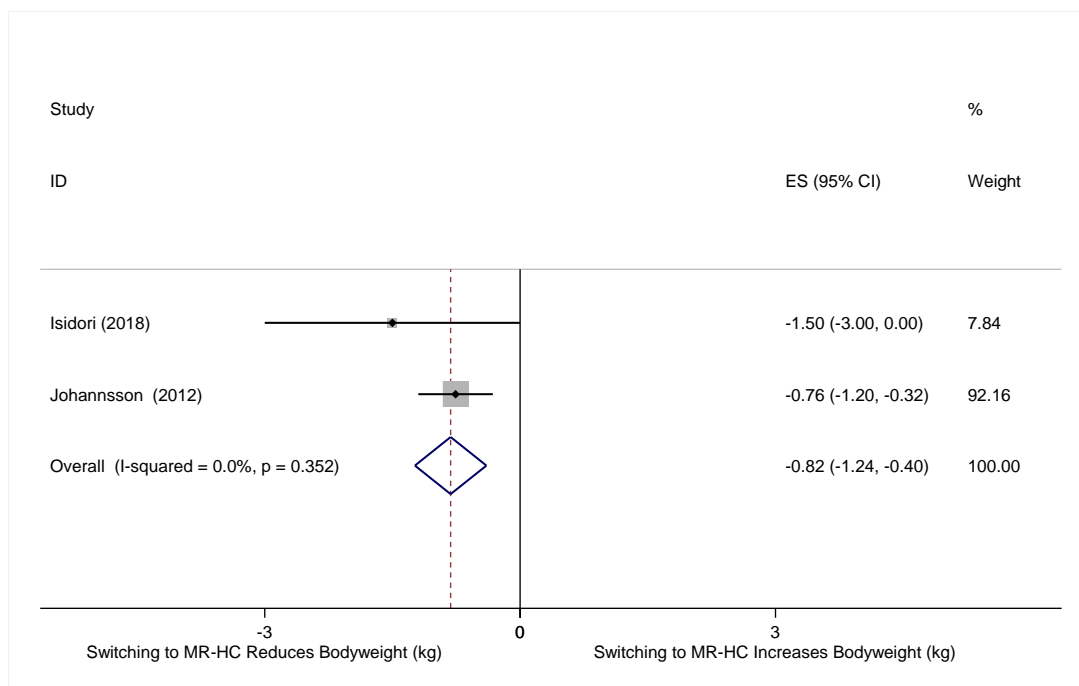
							HbA1c and cholesterol	Data for metabolic outcomes not fully reported.
Guarnotta, 2018 (B) <sup>29</sup>	Retrospective Case Series	Primary and secondary	36 months	Italy	49	BMI; HbA1c; Cholesterol	Significant decrease in BMI and HbA1c.	Low risk across all domains for assessing single arm studies.
Mongioi, 2018 <sup>27</sup>	Prospective Uncontrolled Before and After Study	Primary and secondary	12 months	Italy	19	BMI; HbA1c; Cholesterol	No significant change in BMI or cholesterol; significant decrease in HbA1c in primary adrenal insufficiency patients.	High Risk of bias in ascertainment. Includes treatment naïve patients with no prior exposure to glucocorticoids.



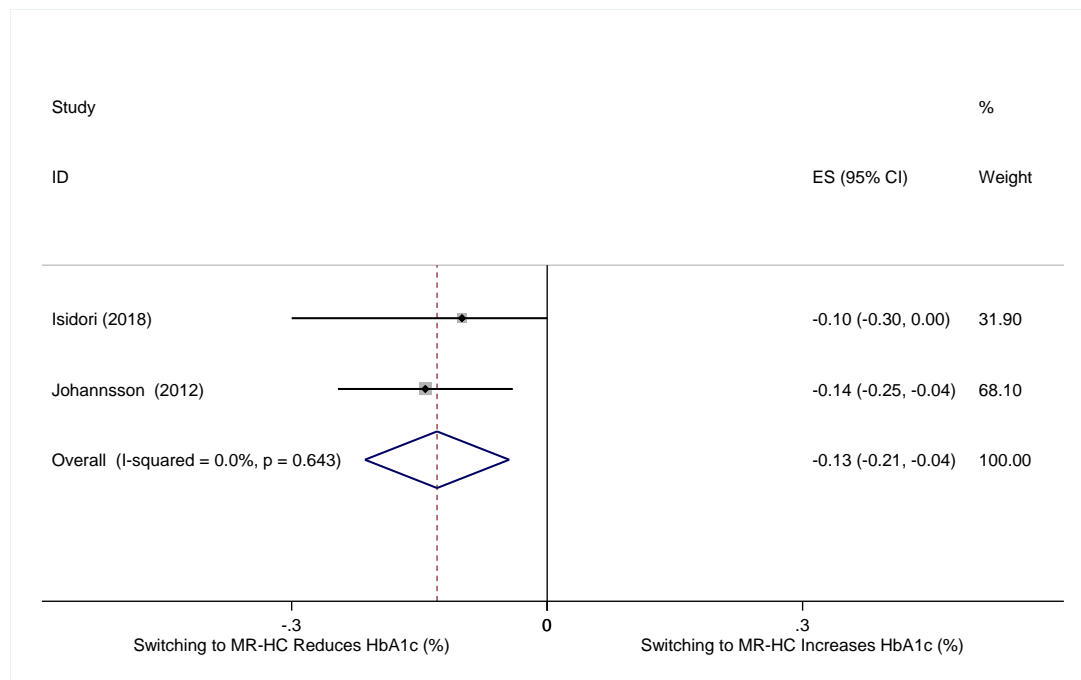
**Figure 2 - Meta-Analysis Graphs of Randomised Control Trials at 3 months**



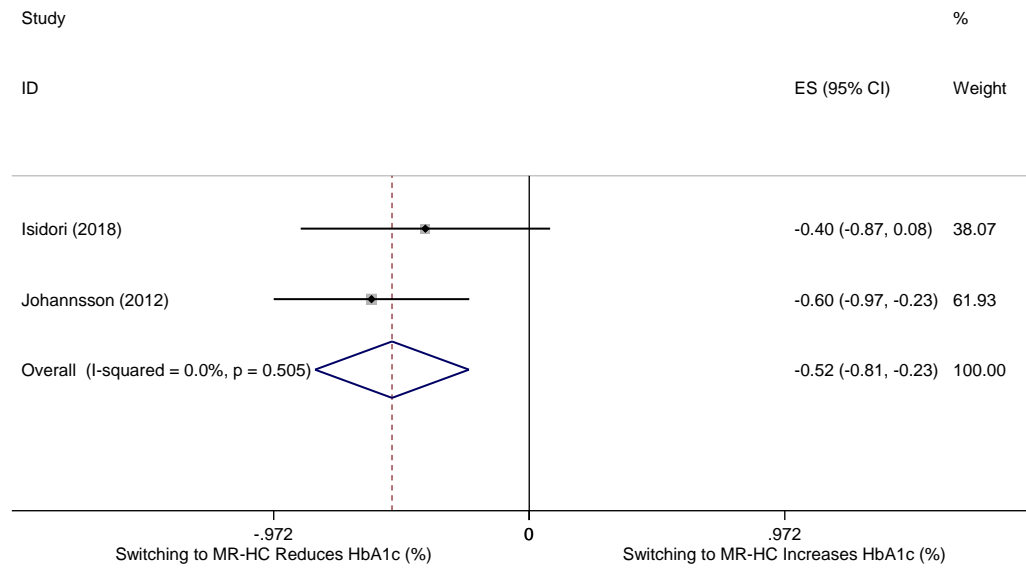
**Figure 2A: Forest Plot of Randomised Controlled Trials at 3 months of change in BMI (kg/m<sup>2</sup>) post switching from standard glucocorticoid replacement to once daily MR-HC**



**Figure 2B: Forest Plot of Randomised Controlled Trials at 3 months of change in Bodyweight (kg) post switching from standard glucocorticoid replacement to once daily MR-HC**

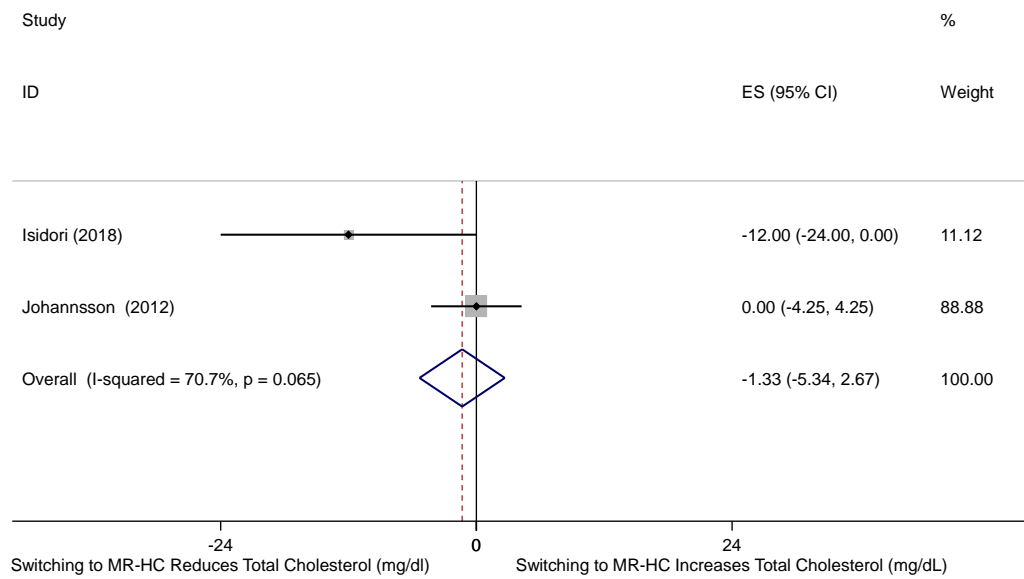


**Figure 2C: Forest Plot of Randomised Controlled Trials at 3 months of change in HbA1c (%) in all patients post switching from standard glucocorticoid replacement to once daily MR-HC**

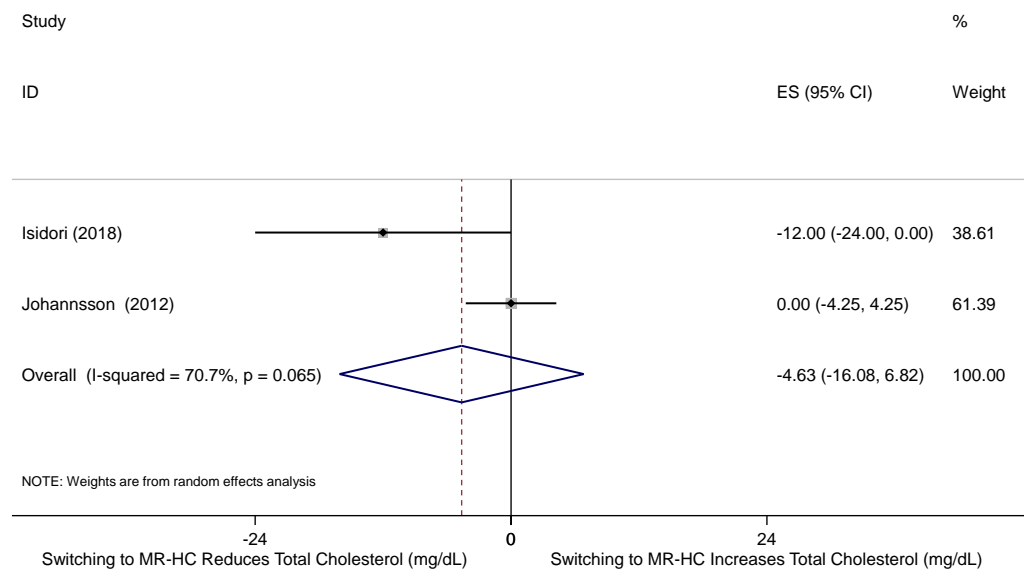


**Figure 2D: Forest Plot of Randomised Controlled Trials at 3 months of change in HbA1c (%) in diabetic patients post switching from standard glucocorticoid replacement to once daily MR-HC**

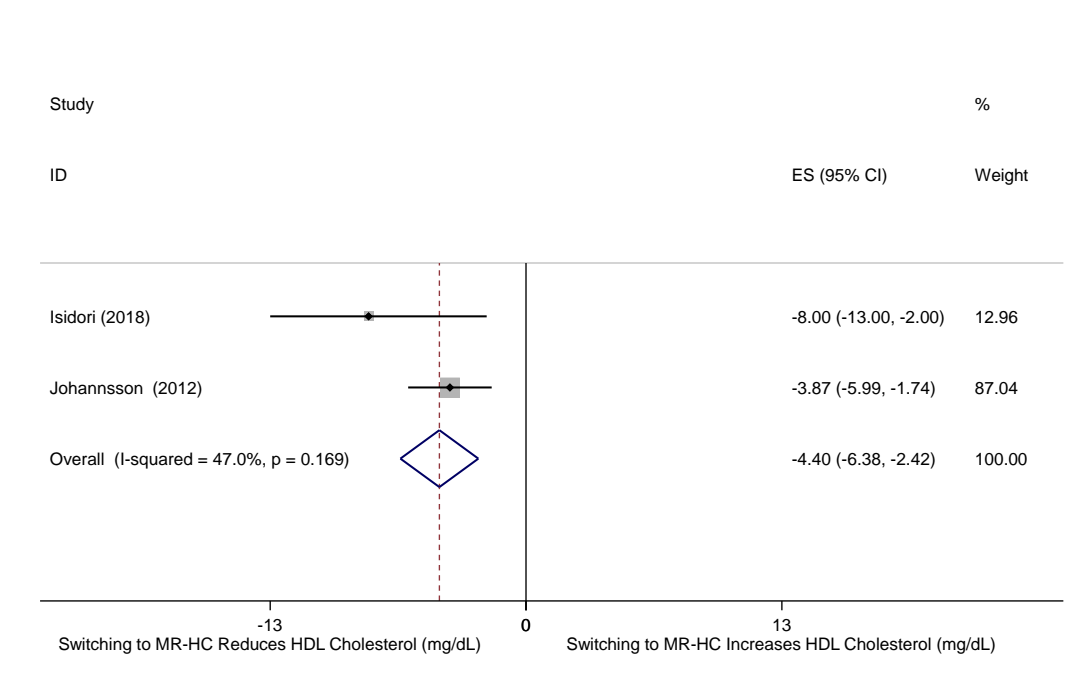
## Meta-Analyses of Secondary Outcomes in Randomised Trials



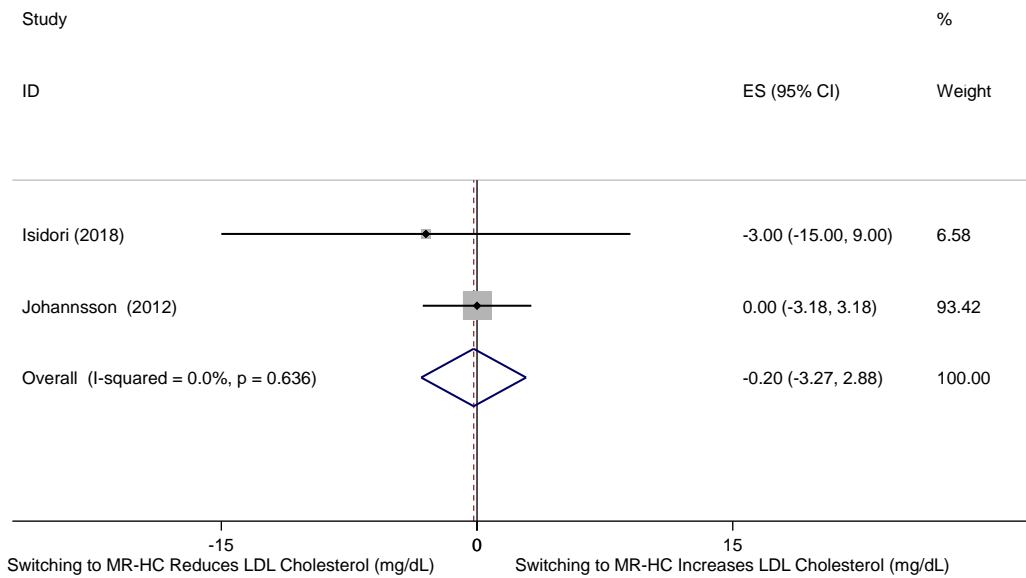
**Figure 3A: Forest Plot of Randomised Controlled Trials at 3 months of change in total cholesterol (mg/dL) in fixed effects meta-analysis post switching from standard glucocorticoid replacement to once daily MR-HC**



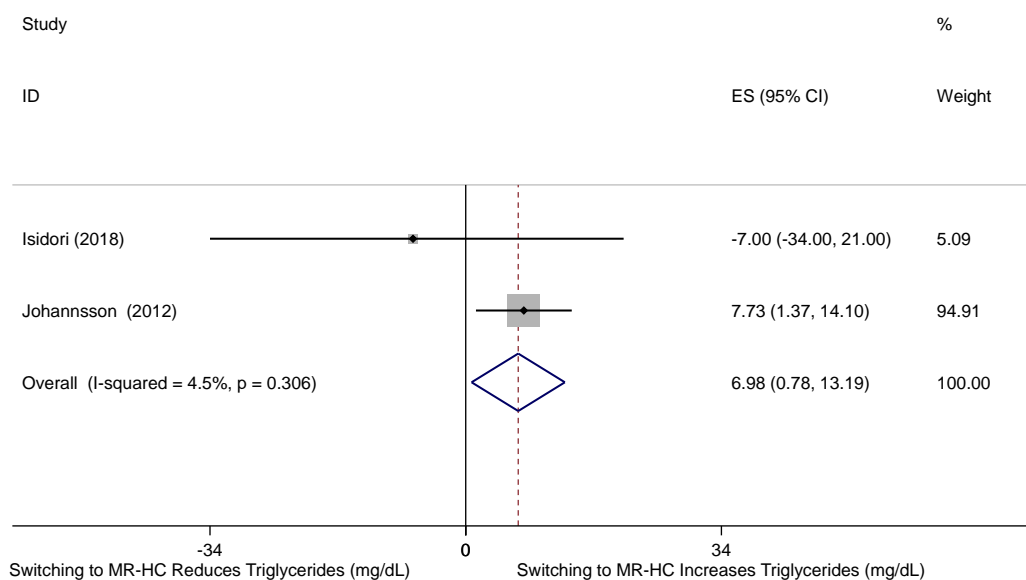
**Figure 3B: Forest Plot of Randomised Controlled Trials at 3 months of change in total cholesterol (mg/dL) in random effects meta-analysis post switching from standard glucocorticoid replacement to once daily MR-HC**



**Figure 4A: Forest Plot of Randomised Controlled Trials at 3 months of change in HDL cholesterol (mg/dL) in fixed effects meta-analysis post switching from standard glucocorticoid replacement to once daily MR-HC**



**Figure 4B: Forest Plot of Randomised Controlled Trials at 3 months of change in LDL cholesterol (mg/dL) in fixed effects meta-analysis post switching from standard glucocorticoid replacement to once daily MR-HC**



**Figure 4C: Forest Plot of Randomised Controlled Trials at 3 months of change in triglycerides (mg/dL) in fixed effects meta-analysis post switching from standard glucocorticoid replacement to once daily MR-HC**

**Table 3 - Data Extracted of Primary Outcomes from Non-randomised control trials**

Author, year (reference), Treatment group	Follow up time point	Baseline BMI (kg/m <sup>2</sup> )	Follow up BMI (kg/m <sup>2</sup> ) [p value]	Baseline HbA1c (%)	Follow up HbA1c (%) [p value]	Baseline Total Cholesterol (mg/dL)	Follow up Total Cholesterol (mg/dL) [p value]	Baseline LDL Cholesterol (mg/dL)	Follow up LDL Cholesterol (mg/dL) [p value]	Baseline HDL Cholesterol (mg/dL)	Follow up HDL Cholesterol (mg/dL) [p value]	Baseline Triglycerides (mg/dL)	Follow up Triglycerides (mg/dL) [p value]
Quinkler, 2015, <sup>25</sup> Control	338 days (98-498)*	25.7 (1.14)†	25.8 (1.08) † [p=0.887]	5.63 (0.13) †	5.72 (0.15) † [p=0.975]	221.8 (10.8) †	210.9 (13.1) † [p=0.332]	133.9 (9.1) †	128.4 (11.1) † [p=0.925]	62.5 (4.3) †	61.2 (5.0) † [p=0.306]	149.3 (16.4) †	173.4 (26.7) † [p=0.820]
Quinkler, <sup>25</sup> MR-HC group	128 days (68-429)*	26.0 (0.75) †	25.6 (0.71) † [p=0.003]	6.04 (0.29) †	5.86 (0.28) † [p=0.014]	213.8 (7.97) †	200.1 (7.57) † [p=0.016]	127.2 (7.6) †	121.4 (7.0) † [p=0.060]	65.4 (3.5) †	62.7 (3.3) † [p=0.190]	115.7 (11.9) †	120.9 (11.3) † [p=0.605]
Guarnotta, <sup>30</sup> 2019, (A) Control	48 months	25.9 (0.77) ‡	28.0 (0.80) ‡ [p<0.001]	34.8 (3.33) ‡	43.1 (1.52) ‡ [p=0.020]	193.4 (4.23) ‡	195.7 (4.00) ‡ [p=0.136]	100.7 (34.7) ‡	117.0 (29.3) ‡ [p=0.018]	60.2 (20.8) ‡	56.0 (12.7) ‡ [p=0.137]	54.4 (29.3) ‡	57.1 (27.8) ‡ [p=0.131]
Guarnotta, <sup>30</sup> 2019, (A)	48 months	27.6 (0.68) ‡	26.6 (0.70) ‡ [p=0.002]	48.7 (2.32) ‡	39.1 (1.22) ‡ [p<0.001]	210.4 (6.95) ‡	182.2 (3.82) ‡ [p=0.006]	118.9 (38.2) ‡	95.0 (26.6) ‡	58.7 (18.5) ‡	61.0 (15.1) ‡	61.8 (29.3) ‡	56.7 (32.0) ‡



MR-HC group									[p=0.005]		[p=0.284]		[p=0.751]
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\*Expressed as median and range

†Expressed as mean and (standard error)

‡Originally reported as mean and standard deviation, with standard deviation converted to standard error for this table

**Table 4 - Data Extracted of Primary Outcomes from Single Arm Studies**

Author, year (reference)	Follow up time point	Baseline BMI (kg/m2)	Follow up BMI (kg/m2) [p value]	Baseline HbA1c (%)	Follow up HbA1c (%) [p value]	Baseline Total Cholesterol (mg/dL)	Follow up Total Cholesterol (mg/dL) [p value]	Baseline LDL Cholesterol (mg/dL)	Follow up LDL Cholesterol (mg/dL) [p value]	Baseline HDL Cholesterol (mg/dL)	Follow up HDL Cholesterol (mg/dL) [p value]	Baseline Triglycerides (mg/dL)	Follow up Triglycerides (mg/dL) [p value]
Giordano, 2016, <sup>28</sup>	12 months	24.37 (18.71-31.83)* <sup>^</sup>	24.02** Reported non-significant (p<0.05)	6.0 (4.3-7.7)	6.2 (4.3-8.9) [p=0.002]	208.0 (145.0-271.0)	172.0 (120.0-229.0) Reported significant [p<0.05]	107.4 (59.6-173.6)	85.6 (51.4-152.0) Reported significant [p<0.05]	70.3 (46.7 - 100.2) * <sup>^</sup>	65.1** Reported non-significant (p<0.05)	101.4 (43.1 - 187.5) * <sup>^</sup>	79.9 ** Reported non-significant (p<0.05)
Ceccato, 2018, <sup>24</sup>	8 months (6-12 months)	24.3 (22.4-30.6)-	23.5 (21.0-26.0) - [p=0.929]	5.7 (5.3-7.5) -	5.5 (5.4-6.8) - [p=0.27]	231.2 (189.5-270.2) -	211.5 (189.9-216.1) - [p=0.048]	120.0 (108.9-204.6) -	116.6 (105.3-141.7) - [p=0.285]	49.0 (44.0-71.8) -	60.6 (48.6-78.4) - [p=0.715]	66.0 (36.3-108.1) -	58.3 (42.5-110.0) - [p=0.963]
Frara, 2018, <sup>26</sup>	24 months	28.3 (20.0-32.4)*	Not reported	5.9 (5.1-6.5)*	Reported non-significant	202 (166-253)*	Reported non-significant	102 (41-173)*	Reported non-significant	65 (36-135)*	Reported non-significant	152 (105-214)*	Reported non-significant

					significant [p=0.28]		[p=0.51]		[p=0.26]		[p=0.76]		[p=0.22]
Guarnotta, 2018, (B)  Normal Glucose Tolerance <sup>29</sup>	36 months	25.1 (2.52) ‡	23.7 (0.84) ‡ <sup>^</sup> [p=0.017]	5.5 (0.08) ‡	5.2 (0.20)‡ <sup>^</sup> [p=0.034]	207.1 (6.72) ‡	Not reported - stated non- significant  (p<0.05)	119.5 (7.18) ‡	Not reported - stated non- significant  (p<0.05)	59.2 (3.64) ‡	54.0 (1.89) ‡ <sup>^</sup> [p=0.036]	141.1 (15.5) ‡	Not reported - stated non- significant  (p<0.05)
Guarnotta, 2018, Pre- Diabetes <sup>29</sup>	36 months	32.6 (1.08) ‡	29.1 (0.86) ‡ <sup>^</sup> [p<0.001]	5.8 (0.12) ‡	5.5 (0.18)‡ <sup>^</sup> [p=0.001]	235.1 (48.0) ‡	Not reported - stated non- significant  (p<0.05)	146.8 (12.6) ‡	Not reported - stated non- significant  (p<0.05)	53.6 (2.88) ‡	‡ <sup>^</sup> [p=0.043]	172.8 (35.3) ‡	Not reported - stated non- significant  (p<0.05)
Mongioli, 2018,  Primary Adrenal Insufficiency <sup>27</sup>	12 months	28.8 (1.45) <sup>^</sup> †	27.7 (1.35) <sup>^</sup> † Reported non- significant  (p>0.05)	6.28 (0.31) <sup>^</sup> †	5.01 (0.26) <sup>^</sup> † Reported significant  (p<0.05)	191.6 (9.05) <sup>^</sup> †	181.7 (14.8) <sup>^</sup> † Reported non- significant  (p>0.05)	120.8 (5.7) <sup>^</sup> †	114.6 (8.8) <sup>^</sup> † Reported non- significant  (p>0.05)	43.4 (2.0) <sup>^</sup> †	49.4 (3.8) <sup>^</sup> † Reported non- significant  (p>0.05)	192.6 (13.9) <sup>^</sup> †	160.2 (15.7) <sup>^</sup> † Reported significant  (p<0.05)
Mongioli, 2018, Secondary	12 months	30.36 (1.55) <sup>^</sup> †	30.7 (1.55) <sup>^</sup> †	5.80 (0.33) <sup>^</sup> †	5.63 (0.29) <sup>^</sup> †	231.9 (12.3) <sup>^</sup> †	200.7 (15.6) <sup>^</sup> †	145.5 (7.2) <sup>^</sup> †	128.0 (9.8) <sup>^</sup> †	51.8 (2.5) <sup>^</sup> †	45.0 (3.6) <sup>^</sup> †	220.4 (17.6) <sup>^</sup> †	266.7 (26.9) <sup>^</sup> †

Adrenal Insufficiency <sup>27</sup>			Reported non-significant (p>0.05)		Reported non-significant (p>0.05)		Reported non-significant (p>0.05)		Reported non-significant (p>0.05)		Reported non-significant (p>0.05)		Reported significant (p<0.05)
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^Extracted data from published graph using WebPlotDigitizer<sup>19</sup>

\*Expressed as median and range

\*\*Reported as median, range not extractable from graph using WebPlotDigitizer<sup>19</sup>

†Expressed as mean and standard error

-Expressed as median and inter-quartile range

‡Originally reported as mean and standard deviation, with standard deviation converted to standard error for this table

## Supplementary Appendix

### Search Strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to July 19, 2019>

Search Strategy:

-----

- 1 exp Adrenal Insufficiency/ (12244)
- 2 exp ADDISON DISEASE/ (4631)
- 3 exp Hypopituitarism/ (8996)
- 4 (Adrenal\* and insufficien\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (12873)
- 5 addison\*.mp. (6180)
- 6 hypopituitar\*.mp. (9214)
- 7 1 or 2 or 3 or 4 or 5 or 6 (29263)
- 8 exp Glucocorticoids/ (186805)
- 9 exp HYDROCORTISONE/ (71612)

- 10 exp CORTISONE/ (19554)
- 11 exp PREDNISOLONE/ (49837)
- 12 (Glucocorticoid\* or hydrocortisone\* or prednisolone\* or cortisone\*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (226891)
- 13 8 or 9 or 10 or 11 or 12 (308920)
- 14 7 and 13 (6829)
- 15 plenadren.mp. (10)
- 16 Chronocort.mp. (10)
- 17 exp Delayed-Action Preparations/ (45544)
- 18 ((Dual or Modified or Delayed or Sustained) and Release).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (77539)
- 19 15 or 16 or 17 or 18 (98948)
- 20 14 and 19 (97)

Database: Embase Classic+Embase <1947 to 2019 July 22>

Search Strategy:

- 
- 1 exp Adrenal Insufficiency/ (13209)
  - 2 exp ADDISON DISEASE/ (7517)
  - 3 exp Hypopituitarism/ (13811)
  - 4 (Adrenal\* and insufficien\*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (22900)
  - 5 addison\*.mp. (9334)
  - 6 hypopituitar\*.mp. (15686)
  - 7 1 or 2 or 3 or 4 or 5 or 6 (43253)
  - 8 exp Glucocorticoids/ (749779)
  - 9 exp HYDROCORTISONE/ (138404)
  - 10 exp CORTISONE/ (38150)
  - 11 exp PREDNISOLONE/ (126581)
  - 12 (Glucocorticoid\* or hydrocortisone\* or prednisolone\* or cortisone\*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (422124)
  - 13 8 or 9 or 10 or 11 or 12 (787106)
  - 14 7 and 13 (16984)
  - 15 plenadren.mp. (38)

- 16 Chronocort.mp. (38)
- 17 exp Delayed-Action Preparations/ (7819)
- 18 ((Dual or Modified or Delayed or Sustained) and Release).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word] (118067)
- 19 15 or 16 or 17 or 18 (118093)
- 20 14 and 19 (228)

\*\*\*\*\*

Date Run: 23/07/2019 15:22:34

Database: Cochrane CENTRAL

ID	Search Hits
#1	Adrenal insufficiency 640
#2	Adrenal* AND insufficien* 1090
#3	Hypopituitary 124
#4	Hypopituitar* 342
#5	#1 OR #2 OR #3 OR #4 1412
#6	MeSH descriptor: [Adrenal Insufficiency] explode all trees 215
#7	MeSH descriptor: [Hypopituitarism] explode all trees 280



#8	#5 OR #6 OR #7	1585	
#9	MeSH descriptor: [Glucocorticoids] explode all trees	4298	
#10	glucocorticoid*	8400	
#11	MeSH descriptor: [Hydrocortisone] explode all trees	5750	
#12	hydrocortisone*	9157	
#13	MeSH descriptor: [Cortisone] explode all trees	127	
#14	cortisone*	599	
#15	MeSH descriptor: [Prednisolone] explode all trees	4504	
#16	prednisolone*	7024	
#17	#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	23634	
#18	#8 AND #17	652	
#19	MeSH descriptor: [Delayed-Action Preparations] explode all trees	6300	
#20	plenadren*	1	
#21	chronocort*	10	
#22	(Dual* OR Modified* OR Delayed* OR Sustained*) AND Release*	11779	
#23	#19 OR #20 OR #21 OR #22	14073	
#24	#18 AND #23	60	

**CINAHL Search Strategy**

#	Query	Limiters/Expanders	Last Run Via	Results
S18	S11 AND S17	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	5
S17	S12 OR S13 OR S14 OR S16	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	6,800
S16	"(Dual or modified or delayed or sustained) and SmartText release"	Search modes - SmartText Searching	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	1,546
S15	"(Dual or modified or delayed or sustained) and SmartText release"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	0

S14	(MH "Delayed- Action Preparations+")	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	6,793
S13	"chronocort"	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	2
S12	"plenadren"	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	1
S11	S9 AND S10	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	601

S10	S1 OR S2 OR S3	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	1,736
S9	S4 OR S5 OR S6 OR S7 OR S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	21,287
S8	"prednisolone"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	3,606
S7	"cortisone"	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL Complete	562

S6	"hydrocortisone"	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	7,145
S5	"glucocorticoids"	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	8,366
S4	(MH "Glucocorticoids+") OR (MH "Cortisone") OR (MH "Hydrocortisone") OR (MH "Prednisone")	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	16,866
S3	"addison"	Search modes - Boolean/Phrase	Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search CINAHL	125

S2	"adrenal insufficiency"	Search Boolean/Phrase	modes - Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,173
S1	(MH "Adrenal Insufficiency+") OR (MH "Addison's Disease")	Search Boolean/Phrase	modes - Database - Complete	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,329

## Risk of Bias Assessments

**Table 1: Risk of Bias Assessments in Randomised Control Trials**

<u>Author, year (reference)</u>	<u>Random Sequence Generation</u>	<u>Allocation concealment</u>	<u>Blinding of Participants</u>	<u>Blinding of Outcome Assessment</u>	<u>Incomplete Outcome Data</u>	<u>Selective Reporting</u>	<u>Other Bias</u>	<u>Overall Judgement</u>
Isidori, 2018, <sup>17</sup>	Low risk	Low Risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk

**Table 2: Risk of Bias Assessment in Randomised Crossover Trials**

<u>Author, year (reference)</u>	<u>Randomisation Process</u>	<u>Deviation from intended intervention</u>	<u>Missing Outcome Data</u>	<u>Measurement of outcome</u>	<u>Selection of Reported Result</u>	<u>Overall Judgement</u>
Johannsson, 2012, <sup>15</sup>	Unclear risk	High risk	Low risk	Low risk	Low risk	Low risk

**Table 3: Risk of Bias Assessments in Non-Randomised Trials**

<u>Author, year (reference)</u>	<u>Representativeness of exposed cohort</u>	<u>Selection of non-exposed cohort</u>	<u>Ascertainment of exposure</u>	<u>Demonstration that outcome not present at start of study</u>	<u>Comparability of cohorts on basis of design/analysis</u>	<u>Assessment of outcome</u>	<u>Follow up long enough</u>	<u>Adequacy of follow up</u>	<u>Overall NOS Score</u>
Quinkler, 2015 <sup>25</sup>	Selected group of volunteers - <b>no stars</b>	Patients selected whether to be exposed or not. <b>(0 star)</b>	Secure records (1 star)	Yes (1 star)	Difference in follow up time between groups; 6 of switch treatment group exposed to prednisolone (0 stars)	Record linkage (1 star)	Yes (greater than 3 months) (1 star)	Sufficient number accounted for (1 star)	5
Guarnotta, 2019 <sup>30</sup>	Patients exposed to MR-HC of greatly different	Drawn from same centre but of different	Secure records (1 star)	Yes (1 star)	Not matched at start of trial for metabolic	Record linkage (1 star)	Yes (1 star)	Sufficient number account	6



	metabolic characteristics <b>(no stars)</b>	baseline characteristics <b>(no star)</b>			outcomes. Clear dose conversions from standard glucocorticoid therapy to MR-HC <b>(1 stars)</b>			ed for <b>(1 star)</b>	
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<u>Author, year (reference)</u>	<u>Selection</u>	<u>Ascertainment</u>	<u>Causality</u>	<u>Reporting</u>	<u>Overall Judgement</u>
Giordano, 2016 <sup>28</sup>	Low risk	Low risk	Low risk	Unclear risk	Low risk
Ceccato, 2018 <sup>24</sup>	Low risk	Low risk	Some concerns	Low risk	Some concerns
Frara, 2018 <sup>26</sup>	Low risk	Low risk	Low risk	High Risk	Some concerns
Guarnotta, 2018 <sup>29</sup>	Low risk	Low risk	Low risk	Low risk	Low risk
Mongioli, 2018 <sup>27</sup>	High risk	High risk	High risk	Low risk	High Risk

**Table 4; Risk of Bias Assessment in Single Arm  
Studies**



## Raw Data Extracted For Meta-Analysis

### Primary Outcomes

Study Author	Year	bodyweight	lci bodyweight	uci bodyweight	nbodyweight	bmi	lci bmi	uci bmi	nbmi
Isidori	2018	-1.5	-3	0	78	-0.7	-1.4	0	78
Isidori	2018	-4	-6.9	-1.1	78	-1.7	-3	-0.5	78
Johannsson	2012	-0.758	-1.19535*	-0.32065*	59	-0.254	-0.3974*	-0.1106*	59

### Secondary Outcomes

Study Author	Year	total cholesterol	lci totchol	uci totchol	hdl cholesterol	lci hdlchol	uci hdlchol	ldl cholesterol	lci ldlchol	uci ldlchol
Isidori	2018	-12	-24	0	-8	-13	-2	-3	-15	9
Isidori	2018	0	-16	15	-9	-15	-3	7	-8	21
Johannsson	2012	0	-4.24519*	4.24519*	-3.867	-5.9896*	-1.7444*	0	-3.18389*	3.18389*

### Separate extraction of diabetic patients

Study	year	hba1c%	lci hba1c	uci hba1c	nhba1c	months
Isidori	2017	-0.395	-0.8693113*	0.079311*	15	3
Isidori	2017	-0.784	-1.0975942*	-0.47041*	15	3
Johannsson	2012	-0.6	-0.971877*	-0.22812*	10	3

\*Initially Reported as Standard Deviation, confidence interval calculated

Johannsson et al. provided additional data of standard deviation of treatment effects. Isidori et al. provided additional data of subgroup of diabetic patients.

Johannsson et al presented data as treatment difference calculated from within individual-comparison of treatments

Isidori et al presented data as treatment difference calculated from ANCOVA analysis adjusted for age, sex, diabetes mellitus, type of adrenal insufficiency, and outcome at baseline (additionally adjusted for smoking status for HbA1c and serum lipids)

### Code used in Stata for meta-analysis

\* this produces BMI meta-analysis

```
metan bmi lcibmi ucibmi if months==3, fixed label(namevar= study, yearvar= year)
favours(Treatment reduces BMI # Treatment increases BMI)
```

\* this produces bodyweight meta-analysis

```
metan bodyweightkg lcibodyweight ucibodyweight if months==3, fixed label(namevar=
study, yearvar= year)favours(Treatment reduces bodyweight # Treatment increases
bodyweight)
```

\* this produces HbA1c meta-analysis for both data sets

```
metan hba1c lcihba1c ucihba1c if months==3, fixed label(namevar= study, yearvar=
year)favours(Treatment reduces HbA1c # Treatment increases HbA1c)
```

\* this produces cholesterol meta-analysis fixed effects\*

```
metan totalcholesterol lcitotchol ucitotchol if months==3, fixed label(namevar=
studyauthor, yearvar= yearpublished)favours(Treatment reduces total cholesterol #
Treatment increase total cholesterol)
```

\* this produces cholesterol meta-analysis random effects\*

```
metan totalcholesterol lcitotchol ucitotchol if months==3, random label(namevar=
studyauthor, yearvar= yearpublished)favours(Treatment reduces total cholesterol #
Treatment increase total cholesterol)
```

\* this produces HDL cholesterol meta-analysis\*

```
metan hdlcholesterol lcihdlchol ucihdlchol if months==3, fixed label(namevar= studyauthor,
yearvar= yearpublished)favours(Treatment reduces HDL cholesterol # Treatment increases
HDL cholesterol)
```

\* this produces LDL cholesterol meta-analysis\*

```
metan ldlcholesterol lcildlchol ucildlchol if months==3, fixed label(namevar= studyauthor,
yearvar= yearpublished)favours(Treatment reduces LDL cholesterol # Treatment increases
LDL cholesterol)
```

\* this produces triglycerides meta-analysis\*

```
metan triglycerides lcitri ucitri if months==3, fixed label(namevar= studyauthor, yearvar=
yearpublished) favours(treatment reduces triglycerides # Treatment increases triglycerides)
```

