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Review

11β-hydroxysteroid dehydrogenase type 1 inhibitor use in human disease-a systematic review and narrative synthesis

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ABSTRACT

Introduction: 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an intracellular enzyme that catalyses conversion of cortisone into cortisol; correspondingly, 11β-HSD1 inhibitors inhibit this conversion. This systematic review focuses on the use of 11β-HSD1 inhibitors in diseases known to be associated with abnormalities in hypothalamic pituitary adrenal (HPA) axis function.
Methods: The databases screened for suitable papers were: MedLine, EMBASE, Web of Science, ClinicalTrials.gov, and Cochrane Central.
Results: 1925 papers were identified, of which 29 were included in the final narrative synthesis. 11β-HSD1 and its inhibitors have been studied in diabetes, obesity, metabolic syndrome (MetS), and Alzheimer's disease (AD). Higher expression of 11β-HSD1 is seen in obesity and MetS, but has not yet been described in obesity or AD. Genetic studies identify 11β-HSD1 SNPs of interest in populations with diabetes, MetS, and AD. One phase II trial successfully reduced HbA1c in a diabetic population, however trials in MetS, obesity, and AD have not met primary endpoints.
Conclusions: Translation of this research from preclinical studies has proved challenging so far, however this is a growing area of research and more studies should focus on understanding the complex relationships between 11β-HSD1 and disease pathology, especially given the therapeutic potential of 11β-HSD1 inhibitors in development.

1. Introduction

The hypothalamic-pituitary-adrenal (HPA) axis is the body's major neuroendocrine system secreting cortisol, a glucocorticoid. When functioning normally cortisol follows a diurnal rhythm with exposure to stress activating the HPA axis to temporarily increase cortisol and then return to baseline via a negative feedback system [1]. Abnormal function, or dysregulation, of the HPA axis is associated with a large number of diseases.

1.1. Cortisol abnormalities in psychiatric and neurological illnesses

In melancholic depression the dexamethasone challenge (whereby exposure to dexamethasone should result in decreased cortisol) results in increased cortisol levels demonstrating an abnormality in HPA axis function [2]. A recent systematic review found that basal cortisol levels vary across studies of depression, with both normal and abnormal levels seen in patients with this condition [2]. This disparity may be due to the heterogeneity of sampling often seen in studies of depression. When looking at an older adult population there is more clarity, with multiple studies reporting significantly increased levels of morning cortisol for older adults with depression compared to older healthy controls [3].

Increased cortisol levels are seen in the manic phase of bipolar disorder, suggesting HPA hyperactivity [4]. Abnormal HPA function has been targeted in treatment trials in mood disorders with mifepristone, a glucocorticoid receptor (GR) antagonist. Mifepristone works to displace cortisol from glucocorticoid receptors thereby moderating the activity of the HPA axis [5]. Trials have focussed on cognitive enhancement in bipolar disorder and schizophrenia, and symptom management of psychotic depression [6]. Mifepristone was associated with improvements in cognition in people with bipolar disorder [7,8] but no change in people with schizophrenia [9]. There have been mixed results when trialled as a treatment for psychotic depression, with results suggesting there may be a strata of patients who will respond best to this treatment [10–13]. There are currently no ongoing trials of GR antagonists for these indications.

Elevated cortisol has been associated with Alzheimer's disease (AD) in many cross-sectional and cohort studies [14] as well as with cognitive decline in preclinical AD [15] and in cognitively healthy older subjects [16–18]. Elevated 11β-HSD1 is seen in the hippocampal and neocortical

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regions associated with ageing and cognitive decline. Studying the HPA axis as a possible treatment target for AD has been gathering traction in recent years, with interventions such as GR antagonists in development alongside work on 11β-HSD1 inhibitors [19].

Research into HPA axis function and Parkinson's disease (PD) is still in its infancy, however early studies suggest this may be an area of interest for future research. Compared to control participants, people with mild to moderate PD had significantly higher levels of morning salivary cortisol [20]. A recent systematic review found significant cortisol elevation in people with PD in half of the studies included, with higher cortisol levels related to worse functional scores, depression, and risk behaviours [21].

HPA axis function in post-traumatic stress disorder (PTSD) has been widely studied with inconsistent study results. People with PTSD appear to have an elevated cortisol response when the HPA axis is activated using psychological stressors [22]. However basal cortisol levels in those with an established PTSD diagnosis demonstrate huge heterogeneity [23]. To understand HPA axis dysfunction in PTSD it is likely necessary to identify subgroups of the population. For example, female participants with PTSD or those who experienced trauma from sexual or physical abuse had significantly lower basal cortisol than in controls [23].Sri Lankan girls who experienced the 2004 tsunami were more likely than boys to have elevated cortisol levels when re-experiencing symptoms [24]. In contrast to this male 9/11 survivors were more likely to have increased cortisol levels when re-experiencing symptoms compared to women with the same experiences [25].

Psychosis is another diagnostic area where research to date has produced conflicting results, with hyperactivity of the HPA axis associated with higher risk states for development of psychosis, but a blunting of cortisol activity demonstrated during psychological stressor tests [26,27]. Similarly generalised anxiety disorders present with a mixed picture in studies completed to date with both hyperactive and hypoactive cortisol reactivity found [28].

1.2. The HPA axis in metabolic syndrome, obesity, diabetes, and hypertension

A recent systematic review and meta-analysis of 27 studies found no overall evidence of an association between basal cortisol levels and metabolic syndrome (MetS) [29]. Despite this many of the component diagnoses of MetS have been associated with dysregulations in cortisol and the HPA axis. Hypercortisolism appears to correlate with abdominal adiposity [30].The relationship is more complex when considering general obesity or body mass index (BMI) with divergent results reported [30]. Abnormal cortisol has been associated both with type 2 diabetes and with the risk of developing type 2 diabetes up to 9 years after the baseline cortisol measurement [31–34]. Hypertension has also been associated with raised evening cortisol levels in men [33].

1.3. 11β-HSD1 inhibitors

Tissue glucocorticoid levels are regulated not only by central HPA axis activity, but also by 11β-hydroxysteroid dehydrogenase enzymes. The type 1 isozyme (11β-HSD1) is abundant in the liver and adipose tissue, as well as the hippocampus and central nervous system [35,36]. 11β-HSD1 amplifies the active glucocorticoid hormone cortisol by catalysing the conversion of inactive cortisone into the active cortisol [35]. A novel class of drugs, the 11β-HSD1 inhibitors, is currently in development for multiple diseases. 11β-HSD1 inhibitors partially inhibit the enzymatic conversion of cortisone to cortisol, thereby adjusting cortisol levels [37]. Inhibitors of 11β-HSD1 are believed to lower cortisol selectively within the tissues without impacting the normal variations of plasma cortisol during stress response.

This review is aimed at understanding 11β-HSD1 inhibitors as one of the potential treatment avenues for HPA axis abnormalities. To the authors' knowledge there are no known systematic reviews of the evidence base for the therapeutic uses of 11β -HSD1 inhibitors; there is a useful summary review highlighting the main areas, which has been utilised as a basis for the search strategies, however whilst it is comprehensive, it is non-systematic in nature and has thus led to this review [38].

2. Methods

The Preferred Reporting for Systematic Reviews and Meta-Analysis (PRISMA) statement was used in the development of this systematic review. It is registered in PROSPERO with number CRD42018100458 (accessible here). A complementary review of animal models took place at the same time, registered on PROSPERO with number CRD42018098953.

2.1. Search strategy, study selection and data extraction

Included in the search were studies that evaluated an 11β-HSD1 enzyme expression, activity, or trial of an 11β-HSD1 inhibitor in any of the following indications: AD, mild cognitive impairment (MCI), PD, diabetes, MetS, hypertension, obesity, hyperlipidemia, anxiety, depression, PTSD, schizophrenia, and cancer in human adults. Disease areas previously associated with abnormal cortisol levels on clinical presentation, were included, with the one exception being cancer. As cortisol is ubiquitous in the human body cancer was included as a disease that may affect any organ or system, to ensure treatment trials in areas outside of the targeted search were not missed. Exclusion criteria were: exclusively subjects under 18 years, toxicology only studies, studies published before 1993 and those not published or accessible in English (as the review team could not read papers in languages other than English). Excluding non-English studies led to 107 references (2.5%) being excluded from the search prior to de-duplication. The search was performed in MedLine, EMBASE, Web of Science, ClinicalTrials.gov and Cochrane Central, with reference lists manually searched. The search strategy used from EMBASE is included in Appendix 1.

Study selection was performed by two independent investigators (SG and DH) in two stages. Initially titles and abstracts were reviewed for suitability, followed by fully text review against the inclusion and exclusion criteria. Conflicts were resolved by discussion and a third reviewer (CWR) was available if needed. Data was extracted by three reviewers (SG, DH and BG) using a standardised form to gather: design, diagnosis, gender, age, intervention name, placebo type, method of randomisation, primary outcome measure, and secondary outcome measures. The Cochrane Risk of Bias Tool for Randomised Controlled Trials [39] and the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies were used to assess risk of bias [40].

3. Results

In total 1925 studies were identified for review, 49 full texts were considered, and 29 articles included in the narrative synthesis. Fig. 1 presents reasons for article exclusion. Included papers reported studies in diabetes, MetS, obesity, and AD. Six of the papers were randomised controlled trials of investigational medicinal products and the remaining 24 reported on gene expression, metabolism or genome wide association studies. Full details of the studies and data extracted are provided in Table 1.

3.1. Tissue and gene expression studies

3.1.1. Obesity

Ten studies looked at 11β-HSD1 expression in participants with obesity. Nine studies used abdominal tissues and one study utilised blood samples [41]. In all but one study [41], 11β-HSD1 expression was higher in participants who were obese compared to lean controls, with higher mRNA levels also seen in multiple studies [42–50]. Four studies identified

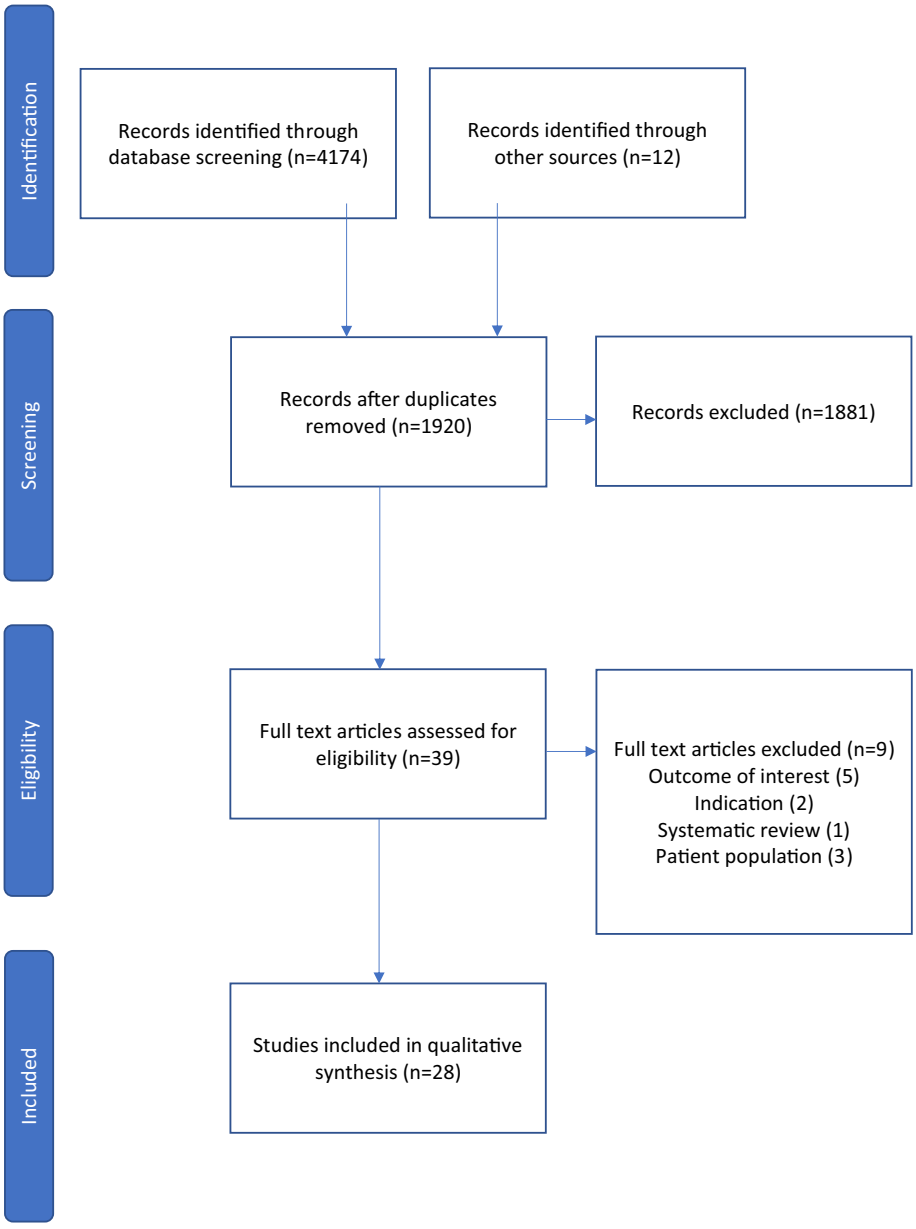

Fig. 1. PRISMA flow diagram.

higher 11β-HSD1 mRNA levels in subcutaneous adipose tissue (SAT) [45,46,49,50], three studies identified higher levels of 11β-HSD1 mRNA in visceral adipose tissue (VAT) [44,47,48] and one study identified higher levels of 11β-HSD1 mRNA in both SAT and VAT [43]. No study reported lower 11β-HSD1 mRNA levels in SAT or VAT in obese populations.

Valsamakis and colleagues found no significant differences in serum 11β-HSD1 expression between lean and obese diabetic men [41]. Shao and colleagues found higher levels of 11β-HSD1 VAT mRNA in obesity compared to controls, with significant associations found between 11β-HSD1 mRNA expression and waist to hip ratio, BMI, homeostasis model assessment-insulin resistance (HOMA-IR), fasting insulin, total cholesterol and triglycerides [42]. Obese women showed a significant increase in 11β-HSD1 mRNA concentrations in both VAT and SAT compared to lean women, with VAT mRNA correlating with BMI, waist circumference, abdominal diameter and percentage fat [43]. In a Chinese population 11β-HSD1 mRNA levels in VAT and SAT correlated with BMI and were both increased in obesity compared to controls [47]. 11β-HSD1 mRNA levels were higher in SAT than VAT in a Chilean population of morbidly obese participants [45]. 11β-HSD1 mRNA levels, and activity [49,50], increased with obesity and correlated with hip, but not waist, circumference [45]. This increase in activity was seen both in Caucasian and Pima Indian populations [50].

Omental tissues from obese participants showed higher 11β-HSD1 mRNA compared to both normal weight controls and participants with Cushing's disease [44]. 11β-HSD1 mRNA correlated with BMI in all subject groups in this study [44]. Data from a subset of participants enrolled in the MONICA project found both higher overall 11β-HSD1 levels and higher 11β-HSD1 mRNA levels were associated with obesity [46]. Overall 11β-HSD1 levels were also associated with hyperinsulinemia in a study of high and low insulin fasting concentrations [46]. A longitudinal study found 11β-HSD1 SAT expression in overweight and obese participants was decreased in with worsening glucose area under curve profiles and increased in those with improving glucose profiles [48], suggested a possible beneficial aspect of higher SAT 11β-HSD1 expression.

3.1.2. Metabolic syndrome and obesity

Two studies reported on 11β-HSD1 expression in participants with co-morbid MetS and obesity. Co-morbid obese and MetS participants

Table 1
Extracted data from studies included in narrative synthesis including description of study design, participants, statistical analysis, outcome measures and results. *ADCS-ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; ADAS-Cog = Alzheimer's Disease Assessment Scale-cognitive subscale; ALT = alanine transaminase; ANHLBI = American Heart Association and National Heart, Lung, and Blood Institute; AU = arbitrary units; AUC = area under curve; BMI = body mass index; CIBIS = Clinician Interview–Based Impression of Severity; DXA = Dual-energy X-ray absorptiometry; FBS = fasting blood sugar; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment-insulin resistance; LDL = low-density lipoprotein; MetS = metabolic syndrome; MMSE = mini mental state examination; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid; NPI: neuropsychiatric inventory; OGTT = oral glucose tolerance test; SAT = subcutaneous adipose tissue; SNP: single nucleotide polymorphism; VAT = visceral adipose tissue.

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
Crowley et al., 2019	Obesity	Analysis of longitudinal 11β-HSD1 activity and expression in overweight and obese participants. Following an overnight fast blood samples were taken, participants underwent a DXA total body scan for body composition analysis, provided a 24 h urine sample and underwent SAT biopsies under local anaesthetic. This was repeated at follow up (3.9 ± 1.5 years)	65 overweight or obese participants, 50.3 ± 7.3 years, 62% male, BMI 33.7 ± 4.3.	Paired *t*-tests, *t*-tests	11β-HSD1 activity and 11β-HSD1 mRNA expression from SAT.	The cohort was divided into decliners and improvers based on change in glucose AUC. There was no relationship seen between urinary 11β-HSD1 activity and longitudinal change in glucose AUC. In contrast 11β-HSD1 mRNA expression in SAT changed over time, with decreased expression in decliners and increased expression in improvers compared to baseline. 11β-HSD1 was the only one of 52 genes studies that was differentially expression in the two groups at follow up (16.8 ± 2.1 vs. 14.4 ± 2.7, $p < 0.05$). Decreasing 11β-HSD1 expression over time was also associated with increasing glucose AUC ($r = -0.4$, $P = 0.04$).
Desbriere et al., 2006	Obesity	Analysis of 11β-HSD1 mRNA levels in lean and obese women. Percentage body fat was assessed by impedancemetry. Abdominal SAT and VAT biopsies were collected via laparotomy or laparoscopy.	22 participants either lean ($n = 10$) or obese ($n = 12$), aged 23–50 years, 100% female. Mean BMI for lean group 21.1 + −0.7 kg/m^2, mean BMI for obese group 37.9 ± 1.5 kg/m^2.	Unpaired student *t*-test, Mann-Whitney U, Wilcoxon, Spearman correlation	Expression of 11β-HSD1 mRNA, biochemical and anthropometric parameters.	In obese patients, 11β-HSD1 mRNA concentrations were increased in both SAT and VAT as compared with lean women (data extracted from graph: subcutaneous: 3.63 AU vs 0.47 AU, $p < 0.05$; visceral: 2.17 AU vs 0.45 AU, $p < 0.05$). The levels of VAT 11-HSD-1 correlating with anthropometric parameters were: BMI ($r = 0.41$, $p = 0.05$), waist circumference ($r = 0.44$, p 0.04), abdominal sagittal diameter (r 0.51, $p = 0.02$), and percentage fat ($r = 0.51$, p 0.02). Although there was a significant difference in age between the groups, there was no effect of age per se on 11-HSD-1 expression ($r = 0.29$, $p = 0.19$ and $r = 0.21$, $p = 0.36$ in SAT and VAT, respectively). There was a significant correlation between 11-HSD-1 and H6PDH mRNA levels in both SAT and VAT ($r = 0.43$, $p = 0.049$, and r = 0.44, $p = 0.042$, respectively)
Lindsay et al., 2003	Obesity	Analysis of 11β-HSD1 mRNA levels in obese Caucasian and Pima Indian participants. Subcutaneous adipose fat biopsies were collected from participants as well as plasma glucose samples and body composition measurements.	19 Pima Indian (10 male, 9 female, age 29.5 ± 7.4 years, BMI 34.6 ± 6.7 kg/m^2), 12 Caucasian (7 male, 5 female, age 27.6 ± 8.1 years, BMI 36.6 ± 8.6 kg/m^2).	Pearson correlation, general linear modelling	11β-HSD1 activity levels, 11β-HSD1 mRNA expression, association with obesity variables	11β-HSD1 activity was significantly associated with BMI (0.68, $p < 0.05$), percentage body fat (0.48, p < 0.05), waist circumference (0.52, p < 0.05), fasting glucose (0.43, p < 0.05), fasting insulin (0.60, p < 0.05) and HOMA-IR (0.70, p < .05). It was not associated with 2-h glucose (0.08, $p > 0.05$). 11β-HSD1 mRNA expression was significantly

Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
						associated with BMI (0.34, $p < 0.05$), fasting insulin (0.42, $p < 0.05$) and HOMA-IR (0.46, $p < 0.05$). It was not associated with percentage body fat (0.15), waist circumference (0.26), fasting glucose (0.19) or 2-h glucose (0.09), with all *p* values >0.05.
Mariniello et al., 2006	Obesity	Analysis of 11β-HSD1 expression in simple obesity and Cushing's syndrome. Participants provided omental tissue, body composition data (weight, height, BMI), blood pressure recorded and blood sample for biochemical analysis.	24 participants, BMI of ≤25 kg/m^2 was classified as normal, 25–30 kg/m^2 overweight and ≥30 kg/m^2 obese.	ANOVA	Expression of 11β-HSD1 mRNA	Obese participants had significantly higher 11β-HSD1 mRNA levels compared to controls and Cushing's participants (13.62 ± 0.15 vs 17.31 ± 0.58 vs 17.37 ± 0.68, $p = 0.001$). There was a significant positive correlation between 11β-HSD1 mRNA expression and BMI in all subject groups ($r = 0.734$, $p < 0.001$).
Munoz et al., 2009	Obesity	Analysis of 11β-HSD1 expression in SAT and VAT in a Chilean population and evaluate associations with features of metabolic syndrome. SAT and VAT biopsies were collected during routine surgery. Participants also provided blood samples for biochemical analysis and records were used for demographic and body composition data.	32 morbidly obese participants meeting criteria for surgical treatment for obesity, mean age 44.5 ± 12 years (female), 46.4 ± 16 years (male), 34.4% male.	*t*-test, Man-Whitney, Kruskal-Wallis, Chi square, Fisher exact test, Spearman correlation	Expression of 11β-HSD1 mRNA in adipose tissue, cholesterol, triglycerides, fasting glucose, fasting insulin.	There were higher levels of 11β-HSD1 mRNA in SAT compared to VAT samples (data extracted from graph: 12.42 AU vs 8.07 AU, $p < 0.05$). SAT 11β-HSD1 mRNA levels increased consistently with obesity levels (data extracted from graph: BMI 30–34: 9.43 AU, $p < 0.05$; BMI 35–39: 12.02 AU, $p < 0.05$; BMI 40–49: 19.07 AU, $p < 0.05$) and correlated positively with hip circumference ($r = 0.66$, $p = 0.018$) but not waist circumference ($r = 0.48$, $p \geq 0.05$). There were no changes with VAT with levels of obesity or hip or waist circumference. There were no correlations between SAT and VAT with fasting glucose, triglycerides or HDL. There was no significant difference in SAT and VAT 11β-HSD1 expression between participants with and without metabolic syndrome.
Nixon et al., 2012	Obesity	Evaluation of salicylate in obesity. Participants were randomised to either placebo or salsalate 1 g every 8 h for 2 weeks orally, followed by a 2-week washout period leading to a crossover of treatment.	16 healthy participants with BMI from 20 kg/m^2 to 50 kg/m^2 (average BMI placebo: 31.9 ± 8.0 kg/m^2; salicylate: 32.0 ± 8.0 kg/m^2), mean age 40.1 (± 10) years, 100% male	*t*-test, ANOVA	Waist to hip ratio, percent body fat, systolic and diastolic blood pressure, fasting triglycerides, fasting total cholesterol, fasting LDL, fasting HDL, fasting glucose levels, fasting insulin levels, adipose 11β-HSD1 mRNA	There were no significant differences between treatment groups on any anthropometric or biochemical measures. There were lower levels of 11β-HSD1 mRNA in adipose tissue in participants treated with salicylate compared to placebo (data extracted from graph: 0.65 AU vs 0.99 AU, $p < 0.05$).
Sandeep et al., 2005	Obesity	Evaluation of carbenoxolone on 11β-HSD1 activity and insulin sensitivity in obese men. Obese men were randomised to placebo or carbenoxolone 100 mg every 8 h orally for 7 days,	12 participants, half lean and half obese, age 20–50 years 100% male.	*t*-test, ANOVA	Metabolite excretion, D3 cortisol presence, glucose kinetics, glucose concentration, insulin concentration	Obese subjects had significantly higher total cortisol metabolites and 5βTHE in excretion compared to lean subjects (21.16 ± 1.90 vs 14.04 ± 1.24, $p < 0.01$; 11.89 ± 1.26

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Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
		followed by a 2 week wash out period leading to cross over of treatment. Participants provided 24-h urine collections, fasted blood samples, body composition measurements (height, weight, hip and waist circumference, blood pressure) and euglycemic clamp. Lean participants attended only once for measurements without medication.				vs 4.50 ± 0.58, $p < 0.001$), as well as lower 5αTHF and (5αTHF + 5βTHF)-to-5βTHE (3.62 ± 0.49 vs 5.91 ± 0.63, $p < 0.05$; 0.57 ± 0.11 vs 1.79 ± 0.20, $p < 0.001$). Carbenoxolone treatment did not affect glucose or insulin concentrations, glucose infusion rate, glucose disposal or glucose production rates compared to placebo.
Rask et al., 2002	Obesity	Analysis of 11β-HSD1 expression in adipose tissue in a subgroup of obese participants. Participants provided body composition data, blood tests and subcutaneous fat samples.	14 participants participated in the 11β-HSD1 expression sub-study, median BMI 24.8, no other data provided.	Correlation	11β-HSD1 expression	11β-HSD1 activity increased in subcutaneous fat as obesity increased, correlation between BMI and AUC of enzyme activity ($r = 0.55$, $p < 0.05$).
Shao et al., 2016	Obesity	Analysis of 11β-HSD1 expression in adipose tissue in obese participants. Participants provided body composition data (height, weight, waist and hip circumference, BMI, waist-to-hip ration and blood pressure), and blood samples for biochemical analysis. VAT samples were collected during surgical procedures.	23 participants undergoing abdominal surgery, split into control ($n = 10$, BMI < 28 kg/m2) and obese ($n = 13$, BMI ≥28 kg/m^2), age 32.5 ± 10.1 years (control), 36.3 ± 17.6 years (obese), 39% male.	Spearman correlation	11β-HSD1 expression, waist-to-hip ratio, BMI, HOMA-IR, fasting insulin, cholesterol and triglycerides	mRNA levels of 11β-HSD1 were higher in obese group compared to the control group (data extracted from graph; 145.98% vs 100%, $p < 0.01$). 11β-HSD1 expression was associated with waist-to-hip ratio ($r = 0.5851$, $p < 0.0001$), BMI ($r = 0.4952$, $p < 0.0001$), HOMA-IR ($r = 0.4637$, $p < 0.0001$), fasting insulin ($r = 0.2547$, $p < 0.01$), total cholesterol ($r = 0.1442$, $p < 0.05$) and triglycerides ($r = 0.1974$, $p < 0.01$).
Wake et al., 2003	Obesity	Analysis of transcriptional upregulation of 11β-HSD1 in obesity, associations between 11β-HSD1 and variations in cortisol/cortisone metabolite rate and associations between 11β-HSD1 gene transcription and cortisol intra-adipose levels. Participants provided SAT samples via biopsy, alongside anthropometry, blood pressure and body composition measurements. Participants also underwent euglycemic hyperinsulemic clamps and provided 24 h urine samples.	32 participants representing high and low fasting insulin concentrations and a range of BMIs, recruited as sample from the larger MONICA project, age 53 ± 3 years (male) and 57 ± 3 years (female), 50% male.	*t*-tests, multiple regression	11β-HSD1 activity, 11β-HSD1 mRNA levels	Higher 11β-HSD1 (expressed as area under the curve) was associated with obesity, log fasting hyperinsulinemia and conversion of oral cortisone to plasma cortisol (log) (0.48, $p < 0.05$; 0.44, $p < 0.05$; −0.40, $p < 0.05$, respectively). Higher 11β-HSD1 mRNA levels were associated with obesity (0.63, $p < 0.01$). No other associations of significance were seen with enzyme activity or mRNA levels. Intra-adipose cortisol and cortisone did not correlate with any markers.
Zha et al., 2009	Obesity	Analysis of gene transcription profiles in VAT and SAT for lean and obese participants. VAT and SAT samples were collected during routine surgery. Participants provided fasted blood samples and body composition measurements (BMI, waist and hip circumference, waist-to-hip ratio and blood pressure)	35 participants split into 20 lean (mean BMI 22.7 ± 1.8 kg/m^2, mean age 44.6 ± 14.7 years) and 15 obese (mean BMI 28.2 ± 1.2 kg/m^2, mean age 54.3 ± 10.3), 51% male.	*t*-test, least squares regression	11β-HSD1 mRNA levels	11β-HSD1 mRNA levels were significantly higher in both SAT and VAT compared to lean participants ($p < 0.01$; $p < 0.01$). 11β-HSD1 mRNA level in both SAT and VAT were significantly correlated with BMI across both groups (SAT r2 = 0.262, $p = 0.0038$; VAT r2 = 0.1826, $p = 0.0185$). There were no other correlations with obesity measurements.
Shah et al., 2011	Obesity and hypertension	Evaluation of MK-0736 and MK-0916 in treatment for overweight and obese participant with	734 participants were screened and 249 were randomised. Participants were aged 8–75 with a BMI	ANCOVA	Sitting systolic and diastolic blood pressure (SiSBP and SiDBP), body weight, LDL-C, HDL-C, triglycerides and	Study did not meet primary endpoint and therefore results should be regarded as nominal. Participants

Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
		hypertension. Participants were randomised to placebo, MK-0736 2 mg, MK-0736 7 mg, MK-0916 6 mg once a day for 12 weeks.	of below 41 kg/m^2 with a history of essential hypertension (with a mean SiSBP of <160 mmHg and mean SiDBP 90–140 mmHg).		waist circumference	treated with MK-0736 7 mg did not have a significant difference in trough SiDBP compared to placebo (−2.4 ± 8.1 mmHg vs −0.2 ± 8.7 mmHg, $p = 0.157$). Participants treated with MK-0916 6 mg and MK-0736 2md did have significant reductions in SiDBP compared to placebo (−3.1 ± 7.9 mmHg, $p = 0.042$; −4.2 ± 7.3 mmHg, $p = 0.01$). Participants treated with MK-0736 7 mg had a significant reduction in trough SiSBP compared to placebo (−4.2 ± 12.9 mmHg vs 0.7 ± 12.2 mmHg, $p = 0.46$), no other treatment doses were significantly different to placebo. Body weight was decreased in all treatment groups (MK-0916 6 mg −1.2 kg ±1.8 mmHg, $p < 0.001$; MK-0736 2 mg −0.6 kg ±1.8 mmHg, $p = 0.003$; MK-0736 7 mg −0.9 kg ±2.0 mmHg, $p < 0.001$). Waist circumference was significantly reduced in those treated with MK-0736 2 mg (−1.9 ± 4.9 cm vs 1.2 ± 6.1 cm, $p < 0.001$) and LDL-C and HDL-C was reduced in those treated with MK-0736 7 mg (−5.2 mg/dL ±20.4 vs 5.7 mg/dL ±30.8, $p = 0.005$; −1.8 mg/dL ±6.7 vs 1.5 mg/dL ±5.0, $p = 0.015$). There were no other differences between treatment groups and no changes with any treatment to triglycerides.
Miyamoto et al., 2009	MetS	Analysis of HSD11B1 polymorphisms (+9410 T > A; +17925C > T; +27447G > C) in participants meeting criteria for metabolic syndrome (Japanese criteria), controls and an intermediate group (meeting criteria for neither metabolic syndrome nor control). Participants provided blood samples, blood pressure measurements and anthropometric estimates.	431 participants with metabolic syndrome (age 67.6 ± 9.5 years), 777 control participants (age 59.5 ± 11.5 years) and 1797 participants in intermediate group (68.0 ± 10.0 years).	Paired *t*-test, chi--square test, logistic regression	Associations of SNPs with metabolic syndrome	There was a trend for association between +9410A allele and metabolic syndrome (OR 1.5 (1.0–2.2), $p = 0.041$) however this was not significant after Bonferroni correction was applied. There were no significant associations seen with either +17925C > T; +27447G > C and metabolic syndrome.
Robitaille et al., 2004	MetS	Analysis of 11β-HSD1 genetic polymorphisms and association with metabolic syndrome. DNA was provided by participants for analysis as part of a larger study of 217 French-Canadian men.	36 participants with metabolic syndrome and 2 controls, mean age 42.8 ± 7.9 years, mean BMI 29.6 ± 4.3.	Gene counting method	Frequency of 11β-HSD1 genetic polymorphisms and association with metabolic syndrome	There was no association between the variants and obesity, plasma or glucose insulin in the fasted state or response to an oral glucose tolerance test.
Alberti et al., 2007	MetS and obesity	Analysis of 11β-HSD1 expression in adipose tissue and association with metabolic syndrome and glucose intolerance. Samples	62 obese participants, mean age bariatric group (n = 13) 39.8 ± 9.87 years, mean age periumbilical biopsy group (n = 49) 45.6 ± 11.4. 10	Paired *t*-tests, two sample *t*-test, Pearson's correlation, multiple regression analysis, ANOVA,	Expression of 11β-HSD1 in SAT & VAT, expression of 11β-HSD1 mRNA, MetS related biochemical variables	Expression of 11β-HSD1 mRNA higher in VAT than SAT in 77% of subjects (2.06 ± 0.92 vs 1.39 ± 0.82). Obese participants with

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Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
		were collected during planned bariatric surgery (VAT & SAT, $n = 13$), or via periumbilical biopsy (SAT, $n = 49$). Participants were grouped by presence/absence of metabolic syndrome (NCEP-ATP III criteria).	males, 52 females.	logistic regression		metabolic syndrome had higher levels of 11β-HSD1 expression in SAT (1.8 ± 1.5 vs 1.0 ± 0.4, $p < 0.01$) compared to those with obesity but without metabolic syndrome. 11β-HSD1 expression in SAT correlated positively with fasting glucose($r = 0.487$, $p < 0.0001$), triglycerides ($r = 0.318$, $p < 0.05$) and urinary free cortisol ($r = 0.397$, $p < 0.01$), and negatively with HDL cholesterol ($r = -0.392$, $p < 0.01$). There was no correlation between 11β-HSD1 expression in SAT and waist circumference, BMI, fasting insulin and blood pressure. Fasting glucose and urinary free cortisol were independently related to SAT 11β-HSD1 expression (beta = 0.460, $p < 0.0001$; beta = 0.423, $p < 0.001$). Obese subjects in the third tertile of SAT 11ßHSD1 expression had a higher risk of type 2 diabetes: (OR 9.6, 95% CI 1.0–88.6; $p < 0.05$) and metabolic syndrome (OR 8.0, 95% CI, 1.7–36.7; $p < 0.01$) when compared to the first tertile.
Baudrand et al., 2010	MetS and obesity	Analysis of 11β-HSD1 expression in VAT, SAT and liver in morbidly obese participants to establish presence of correlations with clinical, anthropometric, and biochemical values. Samples (blood and biopsy) collected during surgery from all participants. Participants were defined as having MetS using NCEP-ATP III criteria.	49 participants with morbid obesity undergoing bariatric surgery, 42.1 ± 10.1 years, 29% male, BMI 42.1 ± 6.1, 63% had metabolic syndrome.	Mann-Whitney, Spearman correlation, generalised linear model	Expression of 11β-HSD1 in liver VAT and SAT, correlation of expression with clinical, anthropometric and biochemical variables	There were no differences in 11β-HSD1 expression between participants with and without metabolic syndrome. Hepatic 11β-HSD1 correlated positively with fasting glucose ($r = 0.29$, $p = 0.05$) and ALT ($r = 0.36$, $p = 0.01$) and negatively with BMI ($r = -0.32$, $p = 0.05$). VAT 11β-HSD1 correlated positively with fasting plasma insulin ($r = 0.48$, $p = 0.005$), ALT ($r = 0.36$, $p = 0.02$), total cholesterol ($r = 0.37$, $p = 0.02$) and LDL cholesterol ($r = 0.36$, $p = 0.03$). There were no correlations seen with obstructive sleep apnoea, presence of gallstone disease or fatty liver and no correlations between biochemical variables and SAT levels.
Devang et al., 2017	Type 2 diabetes and MetS	Target SNP association study (rs12086634 and rs846910) with type 2 diabetes and metabolic syndrome in a South Indian population. Participants provided blood for genetic and biochemistry analysis as well as BMI, waist circumference and mid-arm circumference.	616 South Indian participants with either type 2 diabetes (criteria of American Diabetes Association, $n = 207$), or metabolic syndrome (criteria for South Asian population of International Diabetes Federation, $n = 101$) or neither (control group). Mean age ranged from 49.28 to 51.74 years, sex of participants was not provided.	Pearson's k2, two sample *t*-test, logistic regression	Associations of rs12086634 and rs846910 polymorphisms with diagnostic groups	HSD11B1 rs12086634 G allele associated with increased risk of T2D (OR = 1.91, 95% CI-1.33–2.76, $P = 0.0005$) and increased risk of metabolic syndrome, odds ratio 2.37, 95% CI 1.39–4.05, $p = 0.0015$ (and metabolic syndrome OR = 2.37, 95% CI-1.39–4.05, $P = 0.0015$) compared to control group. HSD11B1 rs846910 A allele associated with

Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
						increased risk of T2DM (OR = 1.62, 95% CI-1.02–2.57, $P = 0.03$)
Feig et al., 2011	Type 2 diabetes and MetS	Evaluation of MK-0916 in treatment of type 2 diabetes and metabolic syndrome. Participants were randomised to placebo, MK-0916 0.5 mg, MK-0916 2 mg or MK-0916 6 mg, once daily taken orally for 12 weeks.	154 participants with type 2 diabetes and metabolic syndrome (according to published diagnostic criteria), aged 18–65, 54% male.	ANCOVA	Fasting plasma glucose (primary), A1C, 2-h postprandial glucose, body weight, waist circumference, lipids and blood pressure.	There were no significant differences between any of the groups in fasting plasma glucose or 2 h post-prandial glucose ($p > 0.05$). Participants treated with MK-0916 6 mg had a significant reduction in A1C (−0.08%, $p = 0.049$), body weight (−2.2 kg, $p < 0.001$), systolic blood pressure (−4.6 mmHg, $p < 0.001$), diastolic blood pressure (−3.1 mmHg, $p = 0.001$) and increases in LDL (5.7%, $p = 0.041$) compared to placebo. There were no significant changes with any other doses, and no significant changes to insulin (fed or fasted), waist circumference, HDL-C or triglycerides.
Valsamakis et al., 2004	Type 2 diabetes mellitus and obesity	Analysis of 11β-HSD1 activity in patients, lean and obese, with type 2 diabetes mellitus. Participants provided anthropometric measurements, blood samples for biochemistry, 24 h urine sample and a sub-group underwent abdominal MRI	33 diabetics participants (mean age 44.2 ± 13 years, mean BMI 31.1 ± 7.5 kg/m^2) and 38 healthy participants (mean age 41.4 ± 14 years, mean BMI 38.2 ± 12.8 kg/m^2)	Students *t*-test, Mann-Whitney U	11β-HSD1 activity	There were no significant differences in 11β-HSD1 activity between those with diabetes and controls.
Andrews et al., 2003	Diabetes	Evaluation of the mechanism of action of carbenoxolone on insulin and the effects of carbenoxolone in patients with type 2 diabetes. Participants were randomised to placebo or carbenoxolone 100 mg for 7 days, followed by a minimum 3 month wash out period leading to cross over of treatment. Participants were dosed orally every 8 h.	12 participants were recruited, 6 with type 2 diabetes and 6 healthy controls. All participants were male. Participants with diabetes were diagnosed <3 years previously with type 2 diabetes mellitus by WHO criteria and were not treated apart from with diet. Healthy controls had no diabetes and were matched diabetes group in age, weight, height, BMI and blood pressure	Paired and unpaired *t*-tests, multiple regression.	Glucose production and glycogenolysis	Glucose production from 12.00–12.30 was significantly lower in diabetic subjects on carbenoxolone compared to placebo ($p < 0.05$). There was no difference at other time points. Glycogenolysis from 12.00–12.30 was also significantly lower in diabetic subjects on carbenoxolone compared to placebo ($p < 0.01$). There was no difference at other time points. There was no difference between glucose disposal or gluconeogenesis for either treatment or diagnostic group.
Heise et al., 2014	Type 2 diabetes	Evaluation of RO5093151 (RO-151) and RO5027383 (RO-383) as adjunctive treatments to metformin for patients with type 2 diabetes. Participants were randomised to placebo, RO-151 5 mg twice daily, RO-151 200 mg twice daily, RO-383 50 mg four times daily or RO-383 200 mg four times daily orally for 28 days.	110 participants with type 2 diabetes, age 37–65, male and female.	ANOVA	Mean daily blood glucose, fasting plasma glucose, HbA_{1c}	Treatment with RO-151 and RO-383 showed no difference on mean daily blood glucose and fasting plasma glucose compared to placebo, and no significant changes in HbA_{1c}, glucose or insulin compared to placebo. Participants treated with RO-151 200 mg had a significant change in cholesterol compared to placebo (−5 (−11,2) vs 5 (−1, 13), $p < 0.05$), LDL (−6 (−14,3) vs 9 (0,19), $p < 0.05$), Apolipoprotein B (15 (8, 23) vs 23 (16.30), $p < 0.05$) and reduction in body

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Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
						weight (data extracted from graph: day 27: 1.68 kg vs −0.28 kg, $p < 0.05$). Participants treated with RO-838 200 mg had significant changes to triglycerides (40 (22, 60) vs 12 (−3, 29), $p < 0.05$), VLDL (25 (5, 48) vs −13 (−27, 3), $p < 0.05$) and Apolipoprotein C III (32 (19, 45) vs 15 (5,27), $p < 0.05$)
Jang et al., 2007	Type 2 diabetes	Analysis of 11β-HSD1 and 11β-HSD2 mRNA expression in skeletal muscle of diabetic participants compared to controls. Participants fasted overnight for 10 h prior to collection of blood samples. Body composition measurements collected (body weight, BMI and waist-to-hip ratio). Muscle tissue collected via biopsy of vastus lateralis under sedation.	24 participants, type 2 diabetes (n = 12) or age % sex matched controls (n = 12), aged 57.8 ± 3.27 years (controls) and 58.3 ± 1.58 years (diabetic), 50% male.	Repeated measures ANOVA, Pearson correlation, unpaired t-test	Expression of 11β-HSD1, 11β-HSD2 mRNA and enzyme activity.	There was no difference in 11β-HSD1 expression between diabetic and control subjects (19.59 ± 0.18 versus 19.52 ± 0.23 p = 0.838). 11β-HSD1 expression was 2.7 fold higher in skeletal muscle compared to 11β-HSD2 expression (19.55 ± 0.14 vs 20.98 ± 0.28, p = 0.006). Basal 11β-HSD1 oxo-reductase activity in intact skeletal muscle was significantly lower in diabetic subjects compared to controls (11.4 ± 2.5% per 200 mg muscle/24 h VS 18.5 ± 2.2% per 200 mg muscle/24 h, p = 0.041). 11ß-HSD1 dehydrogenase activity was significantly higher in the diabetic group compared to controls (5.3 ± 0.6% per 3 mg protein VS 3.3 ± 0.3% per 3 mg protein).
Nair et al., 2004	Type 2 diabetes	Analysis of 11β-HSD1 SNPs and association with type 2 diabetes mellitus in a Pima Indian population. Participants provided body composition measurements and blood samples for genetic analysis.	800 Pima Indians	General linear regression models	Associations between SNP polymorphisms and type 2 diabetes, insulin resistance and obesity	SNP1 (n = 706) and SNP5 (n = 839) were both significantly associated with type 2 diabetes mellitus. This was seen in the additive models (SNP1: OR 1.64 (1.11–2.38), p = 0.01; SNP5: OR 1.34 (1.05–1.72), p = 0.02) and the recessive models (SNP1:OR 1.72 (1.14–2.56), p = 0.01; SNP5: OR 1.79 (1.14–2.8), p = 0.01). Both SNPs were significantly associated with glucose uptake rates (SNP1: p = 0.03; SNP5: p = 0.04) after adjusting for relevant covariates of age, sex, fat percentage and nuclear family membership. SNP1 was also associated with fasting insulin (p = 0.002), 30-min plasma insulin (p = 0.002) and 2-h plasma insulin (p = 0.03) after a 75 g oral glucose tolerance test, as well as fasting insulin (p = 0.02) and early insulin secretion (p = 0.003). There were no significant associations between either SNP and age, percentage body fat, fasting glucose, 30-min glucose, 2-h glucose, glucose disposal rate and hepatic insulin sensitivity.

Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
Rosenstock et al., 2010	Diabetes	Evaluation of INCB13739 in treatment of type 2 diabetes. Participants were randomised to placebo, INCB13729 5 mg, INCB13739 15 mg, INCB13739 50 mg, INCB13739 100 mg, or INCB13739 200 mg, for 12 weeks in addition to ongoing metformin monotherapy.	302 participants with type 2 diabetes, BMI between 25 and 45 kg/m^2, A1C between 7 and 11%, aged 18–75 years and taking metformin on a stable dose for at least 10 weeks.	Linear model	A1C, fasting plasma glucose, lipid profiles, proportion of patients achieving A1C ≤ 7%, HOMA-IR, weight, blood pressure and proportion of patients needing rescue therapy.	Participants treated with INCB13739 100 mg and INCB13739 200 mg had significant reductions in A1C (−0.47%, $p < 0.05$; −0.56%, $p < 0.01$). 25% of participants in 100 mg and 200 mg groups achieved A1C at 12 weeks of equal to or below 7%, compared to 9.5% in placebo group. Participants treated with INCB13739 200 mg had significantly lower fasting plasma glucose (−11.5 ± 6.2 mg/dL, $p < 0.01$, LS mean difference of −24.1 mg/dL, $p < 0.01$) and HOMA-IR (−1.32, $p < 0.05$) compared to placebo but no significant changes in other treatment groups. Participants treated with INCB13739 15 mg, INCB13739 100 mg and INCB13739 200 mg had significant decreases in body weight (−0.6 kg, $p < 0.05$; −1.1 kg, $p < 0.05$; −0.9 kg, $p < 0.05$). Participants with Adult Treatment Panel III defined hyperlipidaemia treated with INCB13739 100 mg showed significant reduction in cholesterol (−16 mg/dL, −6%, $p < 0.05$), LDL (−17 mg/dL, −10%, $p < 0.05$) and triglycerides (−74 mg/dL, −16%, $p < 0.05$) however no other treatment groups had any significant differences to placebo. There were no changes to HDL, free fatty acids, systolic or diastolic blood pressure. The number of patients requiring rescue therapy did not differ between groups.
Sandeep et al., 2004	Diabetes and cognition	Evaluation of carbenoxolone on cognitive function in healthy elderly men and cognitive function and metabolic control in type 2 diabetes. Participants were randomised to placebo or carbenoxolone 100 mg in a crossover trial. Participants completed cognitive assessments at the end of each phase of treatment in both groups.	10 healthy volunteers and 12 participants with diabetes.	Wilcoxon matched pair test, ANOVA, *t*-test	Verbal fluency, visual memory, verbal memory, non-verbal reasoning, attention, processing speed, anxiety and depression, HbA_{1c} levels (diabetes group only)	In the healthy individuals carbenoxolone significantly increased verbal fluency scores (44.2 ± 10.6 vs 40.6 ± 12.4, $p = 0.006$). No effect on visual or verbal memory, non-verbal reasoning, attention nor processing speed. No significant effects on mood metrics. In T2DM group, carbenoxolone had no effect on HBA_{1c}, total cholesterol or HDL cholesterol. There were significant improvements on Auditory Verbal Learning Test (58.8 ± 5.2 vs 55.2 ± 8.0, $p = 0.005$). There was no effect on verbal fluency, Raven's matrices not digit symbol substitution test.
Shukla et al., 2019	Type 2 diabetes mellitus	Analysis of 11β-HSD1 activity in participants with type 2 diabetes mellitus compared to age, gender	60 participants, 30 with type 2 diabetes mellitus and 30 age (diabetes 46 years, controls 40 years), gender	Students *t*-test, one-way and two-way ANOVA, Mann Whitney *U* test,	Delta cortisol (surrogate of 11β-HSD1 activity)	Diabetic participants had higher levels of 11β-HSD1 activity compared to controls (12.29 ± 10.65 vs

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Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
		and BMI matched controls. Participants were treated with 1 mg dexamethasone on the night prior to testing and fasting baseline serum cortisol and glucose samples taken prior to participants being given cortisone acetate (25 mg, oral), with second serum cortisol sample taken after dosing.	(no breakdown given) and BMI (diabetes 25.25, controls 24.65) matched controls.	Wilcoxon Signed Rank, Pearson and Spearmen test, multiple regression		6.68 ± 7.24, $p = 0.022$). When split by age this difference was only seen in those under 35 (13 vs 5.4 μg/dL, p = 0.005). 11β-HSD1 activity was also significantly higher in those with diabetes who exercises compared to controls (15.1 vs 6.2 μg/dL, $p = 0.004$) with no differences between diabetic participants and control participants with sedentary or intermediate physical activity levels. 11ß-HSD1 activity was significantly higher in diabetic participants compared to controls when calorie intake was 1900–2200 (12 vs 8.2μg/dL, p = 0.03), with no significant differences seen at higher or lower calorie intake. The lowest BMI group (<23) also saw significantly higher 11ß-HSD1 activity for diabetic participants compared to controls (14.2 vs 8.9μg/dL, $p = 0.017$), with no differences between normal and overweight groups on BMI.
De Quervain et al., 2004	Alzheimer's disease	Genome wide association study for association of 11 glucocorticoid related genes in patients with Alzheimer's disease and control subjects. Participants provided blood for genetic analysis.	814 participants (351 patients with AD, 463 controls), mean age of AD onset was 67 ± 9 years, MMSE of patients 20 ± 6, 40% of patients were male, mean age of controls 68 ± 9 years, MMSE on controls 29 ± 1, 47% of controls were male.	Set association method	Association of 11β-HSD1 gene with Alzheimer's disease	Of the 11 genes tested, only APOE and HSD11B1 were significantly associated with risk for Alzheimer's disease (p = 0.006). The rare A allele of HSD11B1 (rs846911) was present in 2.9% of AD patients compared to 0.5% of controls ($p = 0.008$).
Marek et al., 2014	Mild to moderate Alzheimer's disease	Evaluation of ABT-384 in treatment of mild to moderate Alzheimer's disease. Participants were randomised to placebo, ABT-384 10 mg, ABT-384 50 mg or donepezil 10 mg once daily taken orally for 12 weeks.	Participants met criteria for probable AD and were aged 55–90 years, with an MMSE score of 10–24 at screening. 327 participants were screened and 267 randomised.	ANCOVA, mixed effects maximum likelihood repeated measures model	ADAS-Cog, MMSE, CIBIS, NPI, ADCS-ADL	Study was prematurely discontinued due to lack of efficacy. There was no significant difference on ADAS-Cog for either ABT-384 dose compared to placebo (LS mean change from baseline = −0.35, $p = 0.72$ (10 mg) and LS mean change from baseline = −0.51, $p = 0.67$ (50 mg)). Both doses of ABT-384 showed worse performance on ADAS-Cog at both Week 4 and Week 8, and no comparable difference at week 12. There were no change to any secondary outcome measures with ABT-384 treatment. There was a significant improvement on ADAS-Cog compared to placebo for donepezil (LS mean change from baseline = −3.06, p = 0.02).
Smit et al., 2007	Alzheimer's disease	Analysis of HSD11B1 polymorphism and diagnosis of Alzheimer's disease. Participants	6105 participants from the Rotterdam study and 403 participants from the Frail Old men study.	Cox proportional hazards models, adjusted for age and sex	HSD11B1 83557insA and dementia incidence	34.6% of the study population were heterozygous carriers of HSD11B1 85,577insA and

Table 1 (*continued*)

Study (Author, date)	Disease	Study design	Participants	Statistical analysis	Outcome measures	Description of findings
		provided blood samples.				4.8% were homozygous carriers. There was no association between carriers and non-carriers for incidence of dementia.

had higher levels of 11β-HSD1 SAT expression and higher levels of 11β-HSD1 mRNA activity compared to obese participants without MetS [51]. A second study found no differences in hepatic expression of 11β-HSD1 in obese participants with and without MetS [52]. Both studies utilised the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria to classify MetS [53]. The studies differed in obesity levels, with only 13 of the 62 participants undergoing bariatric surgery in the first [51] compared to all 49 undergoing bariatric surgery in the second [52]. This makes it difficult to draw direct comparisons between the effect of MetS, in addition to obesity, in these studies.

3.1.3. Metabolic syndrome

Two studies reported on MetS alone, although it should be acknowledged that obesity is a component diagnosis of MetS. In a study of 36 French-Canadian men with MetS and two control participants, researchers found no significant associations between 11β-HSD1 polymorphisms and markers of MetS [54]. A study in a Japanese cohort investigated three HSD11B1 polymorphisms (+9410 T > A; +17925C > T; +27447G > C) in participants meeting criteria for metabolic syndrome ($n = 31$), controls ($n = 777$) and an intermediate group meeting criteria for neither metabolic syndrome nor control group (1797) [55]. Whilst there was an initial trend for association between the +9410A allele and metabolic syndrome this was not statistically significant after Bonferroni correction was applied, and there was no association seen between the other two polymorphisms and metabolic syndrome in this population.

3.1.4. Metabolic syndrome and diabetes

One genome wide association study (GWAS) investigated genetics in both diabetes and MetS compared to controls without either disease. The GWAS reported on HSD11B1 single nucleotide polymorphisms (SNPs) in this population. Nearly a quarter of participants with type 2 diabetes or MetS carried one of the two identified HSD11B1 SNPs (rs12086634 and rs846910) compared to 12–13% of the control population [56]. There were no participants included in the study who had co-morbid MetS and diabetes.

3.1.5. Diabetes

Studies looked at 11β-HSD1 expression and activity, as well as 11β-HSD1 SNPs in participants with type 2 diabetes. There were no differences seen in 11β-HSD1 expression between patients and controls [57]. There were higher levels of 11β-HSD1 activity in both studies that investigated this [57,58], with activity particularly high in participants under 35, those with a BMI under 23, those with daily calorific intake between and those who are physically active [58]. In a study of Pima Indians two SNPs (SNP1 and SNP5) were significantly associated with type 2 diabetes mellitus and insulin resistance but not obesity [59], suggesting an interesting area for future research to understand how these genes influence the development of type 2 diabetes in this population.

3.1.6. Alzheimer's disease

An analysis of 814 participants recruited from memory clinics, 351 of whom had a diagnosis of AD, found that of 11 studied genes, only APOE and HSD11B1 were significantly associated with risk for AD. In particular the rare A allele (rs846911) was present in a significantly higher proportion of AD patients (2.9%) compared to controls (0.5%) [60]. This allele is found in the promotor region for HSD11B1, at 2037 base pairs upstream from the start codon. In a larger sample taken from the Rotterdam study ($n = 6105$) there was no association between another SNP of interest, HSD11B1 83,557insA, and dementia incidence [61]. It is of interest that the HSD11B1 gene was the only gene other than APOE to be associated with AD and would be worth replicating in the Rotterdam study as a larger population would allow us to draw firmer conclusions.

3.1.7. Summary of tissue and gene expression study findings

Overall studies found higher levels of 11β-HSD1 expression in obese compared to non-obese participants. Two studies extended this to include obese participants with MetS and these results were inconclusive. There was some evidence for changes to 11β-HSD1 activity in diabetes. There were mixed results for 11β-HSD1 polymorphisms and diabetes or MetS, whilst two studies investigating genetic associations with AD found the rs846911 SNP was associated with AD risk but the HSD11B1 85,557insA SNP was not.

3.2. Interventional studies

All studies of 11β-HSD1 inhibitors in humans reported below are from phase II testing. No compounds were identified in phase III testing and none have been licensed for treatment to date.

3.2.1. Diabetes

INCB13739 or placebo was given at multiple dosages to patients with type 2 diabetes. In this study the primary outcome measure of HbA_{1c} levels were reduced with the two highest doses of INCB13739 compared to placebo. Secondary outcome measures also showed significant changes, with reductions of fasting plasma glucose, HOMA-IR and body weight [62].

RO-151 or RO-838 were given concomitantly with metformin to patients with type 2 diabetes. This study found no changes in the co-primary outcomes of mean daily plasma glucose or fasting plasma glucose, but did show reductions in body weight, a secondary outcome, at the highest treatment dose of both compounds [63].

One trial was identified on the clinicaltrials.gov website that had been terminated due to poor recruitment, and no papers could be identified reporting further on this compound in humans. The trial was a phase II trial designed to test P2202 for people with type 2 diabetes inadequately controlled with a stable dose of metformin or sulfonylurea or both (ClincalTrials.gov Identifier: NCT01674348).

3.2.2. Metabolic syndrome and diabetes

The compound MK-0916 was trialled in participants with co-morbid type 2 diabetes and MetS. The co-primary outcome measures for this study were fasting plasma glucose and 2-h post prandial glucose, with no differences in either outcome between treatment with MK-0916 and placebo group. On secondary outcome measures at the highest dose of MK-0916 there were reductions in HbA_{1c}, body weight, systolic and diastolic blood pressure and increases in LDL cholesterol [64].

3.2.3. Obesity

MK-0736 was trialled to treat co-morbid obesity and hypertension, with no changes seen between compound and placebo on the primary outcome of systolic blood pressure. On secondary outcome measures there was a decrease in body weight, LDL and HDL cholesterol following treatment with the highest dose of MK-0736 [65], however all secondary outcomes were regarded as non-significant by the study's authors.

Whilst not an 11β-HSD1 inhibitor, a study of salicylate, a lipophilic monohydroxybenzoic acid, as a treatment for obesity showed a reduction in adipose 11β-HSD1 mRNA levels although without changes to any anthropometric or biochemical parameters [66].

3.2.4. Alzheimer's disease

One interventional study enrolled mild-to-moderate AD participants to trial ABT-384. The primary endpoint of this phase II study was change from baseline on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog). There were no differences seen between ABT-384 and placebo on either the primary outcome or any of the secondary outcomes, which included the Mini Mental State Examination (MMSE) and activities of daily living [67]. This trial included an active donepezil arm as well as a placebo arm, and results showed that patients treated with donepezil performed better on the ADAS-Cog compared to placebo.

A phase II trial sponsored by Actinogen Medical Ltd. ongoing at the time of review investigated Xanamem™ in mild-to-moderate AD [68]. This trial has since reported no differences seen between Xanamem and placebo on either the primary outcomes (ADAS-Cog and the Alzheimer's Disease composite score (ADCOMS)) or any of the secondary outcomes, which included the MMSE. Ongoing compound development is now investigating higher doses of the compound [69].

3.2.5. Summary of interventional study findings

INCB13739 successfully reduced HbA_{1c}, fasting plasma glucose and HOMA-IR levels in people with type 2 diabetes, however there is no information available on the continued development of this compound. The other type 2 diabetes studies did not meet primary endpoints but did meet secondary endpoints including reduced body weight, reduced HbA_{1c} and reduced LDL cholesterol. It is interesting that HbA_{1c} levels were reduced in many studies and this may be an endpoint worth considering as a primary outcome for future studies. There was no discernible benefit of using 11β-HSD1 inhibitors as an adjunct therapy to metformin for patients with type 2 diabetes. Although two phase II trials have taken

Table 2
Risk of bias assessment for each included study.Studies in bold indicate studies assessed as having a low risk of bias.

Study (Author, date)	Risk of bias assessment	Information on assessment
Alberti et al., 2007	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Andrews et al., 2003	Moderate	Inadequate information on randomisation, concealment and blinding, no pre-published protocol or registration
Baudrand et al., 2010	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Crowley et al., 2019	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
De Quervain et al., 2004	Moderate	No information on power calculations and no pre-published protocols.
Desbriere et al., 2006	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Devang et al., 2017	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Feig et al, 2011	**Low**	Clearly described the randomisation and blinding process, numbers of participants included at each analysis stage with clear reasons for differences in numbers, adopted a well-accepted primary outcome, and were registered on clinicaltrials.gov prior to starting
Heise et al, 2014	**Low**	Clearly described the randomisation and blinding process, numbers of participants included at each analysis stage with clear reasons for differences in numbers, adopted a well-accepted primary outcome, and were registered on clinicaltrials.gov prior to starting
Jang et al., 2007	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Lindsay et al., 2003	Moderate	Participant recruitment was via media and community recruiters so difficult to judge representativeness of population, no power calculation or pre-published protocol
Marek et al, 2014	**Low**	Clearly described the randomisation and blinding process, numbers of participants included at each analysis stage with clear reasons for differences in numbers, adopted a well-accepted primary outcome, and were registered on clinicaltrials.gov prior to starting
Mariniello et al., 2006	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Miyamoto et al., 2009	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Munoz et al., 2009	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Nair et al., 2004	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Nixon et al., 2012	Moderate	No pre-published protocol
Rask et al., 2002	Moderate	No information on power calculation or pre-published protocol
Robitaille et al., 2004	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Rosenstock et al, 2010	**Low**	Clearly described the randomisation and blinding process, numbers of participants included at each analysis stage with clear reasons for differences in numbers, adopted a well-accepted primary outcome, and were registered on clinicaltrials.gov prior to starting
Sandeep et al., 2004	Moderate	Inadequate information on randomisation, concealment and blinding, no pre-published protocol
Sandeep et al., 2005	Moderate	Inadequate information on randomisation, concealment and blinding, no pre-published protocol
Shah et al, 2011	**Low**	Clearly described the randomisation and blinding process, numbers of participants included at each analysis stage with clear reasons for differences in numbers, adopted a well-accepted primary outcome, and were registered on clinicaltrials.gov prior to starting
Shao et al., 2016	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Shukla et al., 2019	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Smit et al., 2007	Moderate	No information on power calculation or pre-published protocol
Wake et al., 2003	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Valsamakis et al., 2004	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.
Zha et al., 2009	Moderate	No information on numbers of participants considered for enrolment or power calculations and no pre-published protocols.

place of 11β-HSD1 inhibitors in mild-to-moderate AD, neither were successful. Both studies suggest changes to dosage, albeit in different directions, with Marek et al. [67] suggesting a trial with <100% inhibition and Actinogen Medical Ltd. working on higher dose studies [69].

3.3. Carbenoxolone

Carbenoxolone was included in the review as a non-specific 11β-HSD inhibitor and is reported separately for clarity. Three studies looked at the effects of carbenoxolone in humans, with one paper reporting on diabetes, one on diabetes and cognition, and one on obesity.

Treatment of type 2 diabetics with carbenoxolone led to reduced glucose production and lower glycogenolysis in a 30-min midday period, with no difference at other time points and no difference in glucose disposal or gluconeogenesis compared to placebo [70]. Carbenoxolone significantly improved verbal fluency scores in healthy men and verbal memory scores in diabetic men compared to placebo, with no other changes to cognition, depression, or anxiety and no changes to HbA_{1c} levels [71]. The use of carbenoxolone in obesity found no changes between treatment and placebo on glucose or insulin concentrations, glucose infusion rate, glucose disposal, or glucose production rates [72].

Carbenoxolone does not have a clear treatment benefit emerging from these trials, with no effect on obesity, changes at one time point only in diabetes, and limited benefits in cognition, specifically verbal memory and verbal fluency.

3.4. Areas with no research to date

No articles were identified reporting on PD, cancer, depression, anxiety, PTSD, schizophrenia, and bipolar disorder. Whilst there is a body of work looking at 11β-HSD1 in depression, anxiety, and PTSD in preclinical models, there were no papers identified in a human population, and none in either preclinical or human in the diagnoses of schizophrenia, bipolar disorder, or PD, investigating 11β-HSD1. Cushing's syndrome (CS) was deliberately not included as this is a disease where cortisol levels are clinically abnormal, whereas all diseases included in the review have changes to cortisol levels that are typically below the upper limits of normal.

3.5. Risk of bias assessments

Papers included in the review were assessed for risk of bias and all were assessed as low or moderate risk. Low risk studies described randomisation and blinding processes, clearly defined primary outcomes and were registered or had published protocols prior to initiation. Moderate risk studies tended to lack information on number of participants considered for enrolment, power calculations, method of allocation or concealment, blinding (where appropriate) and pre-published protocols. There was limited opportunity to compare between the studies, even within a diagnostic field where there was often heterogeneity in inclusion criteria and primary outcome selection. There remains a lack of replication studies from which to draw firm conclusions. Further information on which papers were assessed at each level is provided in Table 2.

4. Discussion

Studies reporting on 11β-HSD1 expression or inhibitors identify some promising areas for further research, but also highlight areas where potential therapeutic benefit is still not well understood.

Overall results suggest increased levels of 11β-HSD1 expression or activity in obesity. Results are mixed for 11β-HSD1 expression and 11β-HSD1 genetic influence in MetS, diabetes and AD, with further research in more homogenous populations required. Trials of 11β-HSD1 inhibitors have also had mixed success to date, with only one study meeting its primary outcome. Similarly, treatment with carbenoxolone has shown mixed results to date with some changes to cognition and glucose production, but no effects on obesity or other parameters of interest in diabetic participants.

Many of the studies included look at comorbidities between MetS, diabetes and obesity. Trials including participants with such co-morbid diseases are important as they commonly co-occur in patients. However, it is also possible that some of the signals are lost in noise when multiple diseases are expressed at once, and it is therefore difficult to determine the exact effects of 11β-HSD1 inhibitors.

Much of the research to date has developed from promising preclinical studies, with 11β-HSD1 inhibitors successfully trialled in diabetes [73–80], MetS [81–86], obesity [87–90], AD [91–94], and PTSD [95]. Challenges in translation of findings from preclinical studies to clinical trials are well acknowledged with recommendations for more rigorous preclinical trial designs suggested [96]. All preclinical studies cited induced the diseases in murine models. Differences in development and expression of the disease between induced and naturally occurring (particularly in AD) may be one part of the translational challenge. More attention should be paid to this translational gap.

The papers included in this review often included heterogeneous groups of participants, which limits the interpretability of some of the results. Studies on obesity used various definitions of obesity and heterogeneous inclusion criteria. Observational studies often did not report on numbers of participants screened compared to those included or recruitment methods making it difficult to confirm how generalizable the findings would be to the population the participants were drawn from. Most studies did include participants with a mean BMI that would be classified as obese by the World Health Organisation [97], however some included participants who would be categorised as overweight not obese. One of these studies was run in China where there is a reduced cut off recommended for obesity and therefore this study appropriately recruited obese participants in the context of the country wide BMI normative values [98]. Both trials using an 11β-HSD1 inhibitor in AD enrolled participants on the basis on a clinical diagnosis, rather than a biomarker as is becoming increasingly common in AD care and research [99]. There are known variations between clinical diagnosis and histopathological diagnosis on autopsy [100] and therefore without a biomarker it is difficult to be certain these studies included people with a definite AD. An 11β-HSD1 PET tracer has recently been developed and tested successfully in humans for the first time [101]. This development will allow further exploration the presence and pattern of 11β-HSD1 in the human brain and better study these inhibitors in diseases such as AD. It is important for the research community to identify the most appropriate markers of 11β-HSD1 expression and activity to then allow harmonisation across study protocols bringing ease of comparability between study results. Identification of participants with abnormal HPA axis function within these disease classes may also be important to move towards a stratified medicine approach, whereby the 11β-HSD1 inhibitors are trialled in those with a known cortisol abnormality.

Whilst CS was out of scope for this review, refractory CS may be an emerging area of interest 11β-HSD1 inhibitor treatment. There is one ongoing phase I/II trial in Japan assessing the safety and efficacy of an unnamed 11β-HSD1 inhibitor in refractory and subclinical CS, with a primary outcome of glucose AUC after 24 weeks of once a day treatment [102]. This developing area of research will inform whether people with refractory CS could benefit from 11β-HSD1 inhibitor treatment. There may also be cardiac indications for these inhibitors based on work with mineralocorticoid receptor (MR) and GR antagonists. Preclinical studies and clinical studies of mineralocorticoid receptor (MR) antagonists suggest that atherosclerosis and heart failure may be a future therapeutic avenue for exploration [103]. Activation of both (GR) and MR have been associated with cardiac development and cardiac pathology [104]. MR antagonists are already developed as effective heart failure treatments [105] however there are side effects such as hyperkalaemia which cannot be tolerated by patients who would benefit from alternative therapeutic options [106]. These treatments work by preventing MR activity

in cardiomyocytes and macrophages [103]. Our review focused on diseases in which 11β-HSD1 could be implicated and targeted for treatment and as such excluded fetal medicine, however it is important to highlight this as an emerging area of therapeutic interest. 11β-HSD1 is found in fetal membranes (including amnion epithelial cells, fibroblasts and chorion trophoblasts) [107], with expression increasing with gestational age [108]. It is also known that both 11β-HSD1 and cortisol increase at the time of partuition [108]. For a recent review of the potential therapeutic use of 11β-HSD1 inhibitors in preterm birth see Wang et al. [109]. The areas of refractory CS, cardiac medicine and fetal medicine all demonstrate future avenues of exploration for 11β-HSD1 inhibitors.

Finally, the involvement of the HPA axis in the mechanism of action of disease pathology remains unclear in many diseases. It is not yet understood if the disease leads to HPA disruption or vice versa. Whilst it is interesting that cortisol levels are increased in many disease processes, treatment to lower cortisol may not have an impact on the underlying disease if cortisol levels are only a correlative effect and not a critical component of the causative pathway. More studies in animals should look at the evolution of disease with long term cortisol (corticosterone in rodents) measures taken to track when increases occur. Similarly, in humans larger and longer cohort studies are required to understand when cortisol increases relative to disease onset. Only once the results of these studies are available will true understanding of whether management of cortisol levels is able to change the course of a disease. 11β-HSD1 inhibitors may also provide an interesting therapeutic avenue to explore the manipulation and modulation of cortisol levels outside of HPA axis activity. Whilst the HPA axis controls circulating glucocorticoid levels, 11β-HSD1 can act to increase glucocorticoid levels within cells and tissues from intrinsically inert metabolites. The use of 11β-HSD1 inhibitors to therapeutically lower these levels may therefore provide a role independent of the HPA axis. This, alongside the evidence identified from this review, highlights 11β-HSD1 inhibitors are important therapeutics to further develop and study in disease populations.

5. Conclusions

Inhibition of 11β-HSD1 remains a promising area for multiple diseases, particularly diabetes, metabolic syndrome, obesity, and AD. The translation from animal models to human clinical trials has to date been challenging and the underlying mechanistic involvement of the HPA-axis in the course of the identified human diseases needs to be better understood to ensure that inhibition of 11β-HSD1 results in therapeutic and clinically meaningful outcomes. Further, future studies should look at optimising the compounds that move to human testing, identifying appropriate clinically useful endpoints when designing protocols, and identifying the appropriate patient population for inclusion in the studies based on evidence of abnormalities in cortisol metabolism.

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Sarah Gregory: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing - original draft, Project administration. **David Hill:** Formal analysis, Writing - review & editing. **Ben Grey:** Formal analysis, Writing - review & editing. **William Ketelbey:** Conceptualization, Writing - review & editing. **Tamara Miller:** Conceptualization, Writing - review & editing. **Graciela Muniz-Terrera:** Writing - review & editing. **Craig W. Ritchie:** Conceptualization, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

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Contributions of authors

SG designed the protocol, search strategy, completed the search, screened papers, extracted data and drafted the manuscript. DH supported with the search, screening and data extraction, as well as drafting of the manuscript. BG supported with data extraction. CWR supported with the protocol design and search strategy, acted as the independent reviewer for article inclusion if required and supported with drafting of the manuscript. BK and TM reviewed and provided comment on the protocol and manuscript. GMT supported with drafting of the manuscript.

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