National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review B: When to suspect adrenal insufficiency

NICE guideline NG243

Evidence reviews underpinning recommendations 1.2.1 to 1.2.4 and 1.9.6 to 1.9.7 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1.1. Review question

When should adrenal insufficiency be suspected (for example, based on risk factors or symptoms)?

1.1.1. Introduction

Whilst adrenal insufficiency is rare, not diagnosing it has fatal consequences, indeed some patients present with adrenal crisis, hence healthcare professionals should be aware of the risks factors and signs and symptoms associated with this condition.

Primary adrenal Insufficiency: Addis

on's disease is the most common cause in adults, and congenital adrenal hyperplasia is the most common cause in children.

Secondary adrenal insufficiency: caused by inadequate adrenocorticotropic hormone production by the pituitary gland, often because of treatment for pituitary disease, or from pituitary tumours and their treatment)

Tertiary adrenal insufficiency: caused by inadequate corticotrophin-releasing hormone production by the hypothalamus. This can be because of treatment for tumours in the hypothalamus or adjoining structures, or more commonly because of administration of glucocorticoids for more than 4 weeks causing hypothalamic-pituitary-adrenal axis [HPA-axis] suppression). Stopping glucocorticoids abruptly may also cause adrenal insufficiency.

Some medicines may cause adrenal insufficiency, such as opioids, checkpoint inhibitors (used increasingly for treating cancer), and medicines inhibiting cortisol clearance such as antifungals and antiretrovirals.

There are number of signs and symptoms for AI and factors that can cause AI (risk factors); however, their ability to discriminate AI accurately enough to make a differential diagnosis and begin treatment is uncertain. The aim of this review is to determine whether these signs, symptoms and risk factors can be as prompts for health care professionals to consider a diagnosis of adrenal insufficiency to initiate treatment in a timely way to prevent death or significant morbidity.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Adults and children without a diagnosis of adrenal insufficiency
Target condition	Adrenal insufficiency
Index tests	Signs/symptoms: • Low blood pressure (hypotension including postural hypotension) • Hyperpigmentation • Lethargy • Salt craving • Weight loss • Hyponatraemia • Hyperkalaemia • Hypoglycaemia • Nausea • Vomiting • Diarrhoea • Failure to respond to initial treatments.
Exposure	**Risk factors:** Drugs: • checkpoint inhibitors e.g., atezolizumab, avelumab, durvalumab • opioids • glucocorticoid therapy (any route)

	• adrenal enzyme inhibitors: e.g., mitotane ketoconazole, itraconazole, voriconazole, metyrapone, etomidate, aminoglutethimidie, phenobarbital, phenytoin, rifampicin • mifepristone • chlorpromazine • imipramine <u>Co-existing conditions or co-morbidities</u>: • Primary hypothyroidism • Type 1 diabetes • Premature ovarian insufficiency • Autoimmune Polyendocrinopathy Syndrome type 1 • Pituitary tumours • Hypothalamic tumours or disease • Traumatic brain injury (particularly base of skull fracture) • Infections: TB, HIV/AIDS, CMV, fungal infections, syphilis, Lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis <u>Specific to children and neonates:</u> • Prolonged jaundice • Hypoglycaemia • Ambiguous genitalia (in females) • Hypotensive crisis Any of the above, alone or in combination.
Reference standards	Reference standard for signs and symptoms review: • Clinical diagnosis of adrenal insufficiency by a specialist • Short Synacthen Test (standard and low dose) • Insulin tolerance test (insulin hypoglycaemia test)
Confounding factors	Confounding factors for risk factors review: • Any exposure/risk factors listed above. • Age and sex as a minimum.
Statistical measures [or] Outcomes	**For signs and symptoms review:** • Diagnostic accuracy data o Sensitivity (prioritised) o Specificity If no sensitivity or specificity, LR- and LR+ if raw data unavailable and unable to calculate from 2 x 2 table. Diagnostic association of signs and symptoms with a confirmed diagnosis of adrenal insufficiency. Measured by: • Association data o Adjusted hazard ratios, odds ratios or risk ratios. • Discrimination o For example C statistic, area under ROC curve • Calibration o for example calibration slope **For risk factors review:**

	• Diagnosis of adrenal insufficiency as defined by authors and reported as adjusted hazard ratios, odds ratios or risk ratios. • For risk prediction tools: sensitivity, specificity and statistical measures of discrimination and calibration including Area Under the Curve (AUC) for risk tools.
Study design	**For signs and symptoms review:** • Cross sectional (single gate) diagnostic studies • If no or insufficient diagnostic accuracy studies are identified, prospective cohort studies looking at the association between individual or combinations of signs and symptoms (multivariable models/algorithms) and a confirmed diagnosis of adrenal insufficiency. • Systematic reviews of the above **For risk factor review:** • Prospective cohort studies with multivariate analysis. • Systematic reviews of the above. Studies will only be included if key confounders have been accounted for in a multivariate analysis. Key confounders will vary based on each risk factor but should at least include age and sex. Published NMAs and IPDs will be considered for inclusion.

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Diagnostic evidence

1.1.4.1. Included studies

Signs and symptoms

A search was conducted for cross-sectional (single gate) studies reporting the diagnostic accuracy of signs and symptoms to identify whether adrenal insufficiency is present as indicated by the reference standard (clinical diagnosis of adrenal insufficiency by a specialist, short Synacthen test (standard and low dose), or insulin tolerance test).

Six studies were included in the review;[1-5, 7] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below in Table 3-13 and the references are detailed in the References section. Evidence was identified for low blood pressure, hyperpigmentation, lethargy, salt craving, weight loss, hyponatraemia, hyperkalaemia, nausea, vomiting and diarrhoea. A variety of reference standard tests and cut-offs were used to identify adrenal insufficiency and one study used more than one reference standard. Three studies were based on people with HIV/AIDS, one study was based on people with dermatological conditions using topical corticosteroids, one study was based on people with suspected tuberculosis and one study was based on people with liver cirrhosis. No studies were identified in children.

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity/specificity 90% and 70% above which a test would be recommended and 60% and 50% below which a test is of no clinical use.

Risk factors

A search was conducted for prospective cohort studies with multivariable analysis reporting the predictive value of risk factors for adrenal insufficiency. No evidence was identified.

See also the study selection flow chart in Appendix C, sensitivity and specificity forest plots in Appendix E, and study evidence tables in Appendix D.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix I.

1.1.5. Summary of studies included in the diagnostic evidence.

Table 2: Summary of studies included in the evidence review of signs and symptoms.

Study	Population	Target condition	Index test	Reference standard	Comments
Abbott 1995[1]	Adults with HIV (n=49)	Cortisol deficiency	Fatigue (lethargy) Sodium (<135 mmol/1) Potassium (>5 mmol/l)	Rapid ACTH stimulation test (short-duration 250 µg synthetic corticotrophin test): normal response defined as 30 min post stimulation cortisol level ≥450 nmol/L, abnormal response defined as post stimulation cortisol <350 nmol/L and impaired response was any intermediate result	Conducted in UK Study also reports systolic postural drop (≥ 10 mmHg), measured by erect and supine blood pressures, but insufficient data to calculate sensitivity/specificity (data missing) Serious indirectness: population
Casanova-Cardiel 2003[2]	Adults with HIV (n=106)	Adrenal insufficiency	Fatigue (lethargy) Weight loss Salt intake (salt craving) Diarrhoea	Low dose short corticotropin stimulation test. Abnormal response cortisol peak response at 60 min <11 µg with respect	Conducted in Mexico Very serious indirectness: population and reference standard

Study	Population	Target condition	Index test	Reference standard	Comments
			Skin hyperpigmentation Mucoses hyperpigmentation Orthostatic hypotension Hyponatraemia (serum Na < 135 mEq/L) Hyperkalaemia (serum Potassium > 5 mEq/L)	to basal, also analyse the data with three different criteria to define subnormal response to ACTH-stimulation test: 1) twofold value of basal cortisol; 2) any cortisol value above 18 µg/dL; and 3) any cortisol value above 20 µg/dL.	
Hintong 2021[3]	Adults with dermatological conditions using topical corticosteroids (n=42)	Adrenal insufficiency	Lethargy Nausea Hypotension Weight loss	8am cortisol level of <3 µg/dL or peak serum cortisol level <0.6 nmol/L at 20 or 40 minutes after a 18 µg/dl ACTH stimulation test defined as AI	Conducted in Thailand Very serious indirectness: population and reference standard
Mabuza 2020[4]	Tuberculosis-suspect patients (n=75)	Adrenal insufficiency	Hypotension Hyperpigmentation Salt craving Weight loss Nausea Vomiting Tiredness (lethargy)	Low-dose ((1µg/ml intravenously) short corticotropin (Synacthen®) stimulation test: morning serum cortisol of <500 mmol/L	Conducted in South Africa Very serious indirectness: population and reference standard
Naguib 2022[5]	Adults with liver cirrhosis (n=132)	Adrenal insufficiency	Hyponatraemia	Basal and peak cortisol after 60 minutes following the short 250 µg Synacthen	Conducted in Egypt Serious indirectness: population

Study	Population	Target condition	Index test	Reference standard	Comments
				test: basal cortisol of <9µg/dl and/or peak cortisol < 18 µg/dl	
Wolff 2001[7]	Critically ill AIDs patients (n=72)	Abnormal cortisol response to ACTH	Fatigue (lethargy) Weakness (lethargy) Nausea Vomiting Diarrhoea Weight loss	Low-dose ACTH test (1 µg/mL); cortisol <18 mg/dl 30 and 40 minutes after	Conducted in Brazil Study also reports concomitant drug use, but cross-sectional data collection and no multivariable analysis (not extracted) Very serious indirectness: population and reference standard

See Appendix D for full evidence tables.

1.1.6. Summary of the diagnostic evidence

Table 3: Clinical evidence summary: low blood pressure (hypotension inclusion postural hypotension)

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Orthostatic hypotension for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.34 (0.21-0.49)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[c]	Specificity=0.66 (0.53-0.78)	VERY LOW
Orthostatic hypotension for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.31 (0.21-0.42)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Very serious[d]	Specificity=0.57 (0.37-0.76)	VERY LOW
Orthostatic hypotension for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[e]	Sensitivity=0.40 (0.05-0.85)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[c]	Specificity=0.66 (0.56-0.75)	VERY LOW
Orthostatic hypotension for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[e]	Sensitivity=0.33 (0.04-0.78)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[c]	Specificity=0.66 (0.56-0.75)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Orthostatic hypotension for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in adults with dermatological conditions using topical corticosteroids							
1 cross-sectional study	42	Very serious[a]	Not serious	Very serious[f]	Not serious	Sensitivity=0.00 (0.00-0.20)	VERY LOW
		Very serious[a]	Not serious	Very serious[f]	Not serious	Specificity=1.00 (0.86-1.00)	VERY LOW
Systolic hypotension for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected tuberculosis							
1 cross-sectional study	75	Very serious[g]	Not serious	Very serious[h]	Serious[i]	Sensitivity=0.86 (0.67-0.96)	VERY LOW
		Very serious[g]	Not serious	Very serious[h]	Not serious	Specificity=0.11 (0.04-0.23)	LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard).*

[b] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).*

[c] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

[d] *Confidence interval crossed the decision thresholds corresponding to 'high specificity' (70%) and 'low specificity' (50%).*

[e] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[f] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from people taking long term topical steroids to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 5 µg ACTH test).*

[g] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); unclear timing between index test and reference standard and high risk of bias arising from the patient flow (missing data)).*

[h] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from tuberculosis population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml Synacthen test).*

[i] *Confidence interval crossed the decision threshold corresponding to 'high sensitivity' (90%).*

Table 4: Clinical evidence summary: hyperpigmentation

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Skin hyperpigmentation for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	160	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.40 (0.26-0.56)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[c]	Specificity=0.63 (0.49-0.75)	VERY LOW
Mucoses hyperpigmentation for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.06 (0.11-0.18)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.93 (0.84-0.98)	VERY LOW
Skin hyperpigmentation for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.40 (0.29-0.51)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Very serious[c]	Specificity=0.64 (0.44-0.81)	VERY LOW
Mucoses hyperpigmentation for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.04 (0.01-0.11)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[d]	Specificity=0.86 (0.67-0.96)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Skin hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[e]	Sensitivity=0.20 (0.01-0.72)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.60 (0.50-0.70)	VERY LOW
Mucoses hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[e]	Sensitivity=0.20 (0.01-0.72)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.94 (0.88-0.98)	VERY LOW
Skin hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[e]	Sensitivity=0.33 (0.04-0.78)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[d]	Specificity=0.61 (0.51-0.71)	VERY LOW
Mucoses hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data	106	Very serious[a]	Not serious	Very serious[b]	Serious[e]	Sensitivity=0.17 (0.00-0.64)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.94 (0.87-0.98)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
collected cross-sectionally)							
Skin hyperpigmentation for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected tuberculosis							
1 cross-sectional study	75	Very serious[f]	Not serious	Very serious[g]	Very serious[h]	Sensitivity=0.79 (0.59-0.92)	VERY LOW
		Very serious[f]	Not serious	Very serious[g]	Not serious	Specificity=0.26 (0.14-0.40)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard).*

[b] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).*

[c] *Confidence interval crossed the decision thresholds corresponding to 'high specificity' (70%) and 'low specificity' (50%).*

[d] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

[e] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[f] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); unclear timing between index test and reference standard and high risk of bias arising from the patient flow (missing data)).*

[g] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from tuberculosis population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml Synacthen test).*

[h] *Confidence interval crossed the decision thresholds corresponding to 'high sensitivity' (90%) and 'low sensitivity' (60%).*

Table 5: Clinical evidence summary: lethargy

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Lethargy (fatigue ≥2) for diagnosing cortisol deficiency (cortisol <350 nmol/L or indeterminate result after 250µg Synacthen) in people with HIV infection							
1 cross-sectional study	49	Very serious[a]	Not serious	Serious[b]	Very serious[c]	Sensitivity=0.86 (0.57-0.98)	VERY LOW
		Very serious[a]	Not serious	Serious[b]	Not serious	Specificity=0.26 (0.12-0.43)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Lethargy (fatigue ≥3) for diagnosing cortisol deficiency (cortisol <350 nmol/L or indeterminate result after 250µg Synacthen) in people with HIV infection							
1 cross-sectional study	49	Very serious[a]	Not serious	Serious[b]	Not Serious	Sensitivity=0.29 (0.08-0.58)	VERY LOW
		Very serious[a]	Not serious	Serious[b]	Serious[d]	Specificity=0.74 (0.57-0.88)	VERY LOW
Lethargy (fatigue) for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[e]	Serious[f]	Sensitivity=0.72 (0.57-0.84)	VERY LOW
		Very serious[a]	Not serious	Very serious[e]	Not serious	Specificity=0.32 (0.21-0.46)	VERY LOW
Lethargy (fatigue) for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[e]	Not Serious	Sensitivity=0.74 (0.63-0.84)	VERY LOW
		Very serious[a]	Not serious	Very serious[e]	Serious[g]	Specificity=0.43 (0.24-0.63)	VERY LOW
Lethargy (fatigue) for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[e]	Serious[f]	Sensitivity=0.40 (0.05-0.85)	VERY LOW
		Very serious[a]	Not serious	Very serious[e]	Not serious	Specificity=0.29 (0.20-0.39)	VERY LOW
Lethargy (fatigue) for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[e]	Serious[f]	Sensitivity=0.33 (0.04-0.78)	VERY LOW
		Very serious[a]	Not serious	Very serious[e]	Not serious	Specificity=0.28 (0.19-0.38)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Lethargy for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in adults with dermatological conditions using topical corticosteroids							
1 cross-sectional study	42	Very serious[a]	Not serious	Very serious[h]	Not serious	Sensitivity=0.00 (0.00-0.20)	VERY LOW
		Very serious[a]	Not serious	Very serious[h]	Not serious	Specificity=0.96 (0.80-1.00)	VERY LOW
Lethargy (tiredness) for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected tuberculosis							
1 cross-sectional study	75	Very serious[i]	Not serious	Very serious[j]	Not serious	Sensitivity=0.25 (0.11-0.45)	VERY LOW
		Very serious[i]	Not serious	Very serious[j]	Not serious	Specificity=0.85 (0.72-0.94)	VERY LOW
Lethargy (fatigue) for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	63	Very serious[k]	Not serious	Very serious[l]	Very serious[c]	Sensitivity=0.75 (0.43-0.95)	VERY LOW
		Very serious[k]	Not serious	Very serious[l]	Serious[g]	Specificity=0.47 (0.33-0.62)	VERY LOW
Lethargy (weakness) for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	63	Very serious[k]	Not serious	Very serious[l]	Serious[f]	Sensitivity=0.42 (0.15-0.72)	VERY LOW
		Very serious[k]	Not serious	Very serious[l]	Serious[g]	Specificity=0.49 (0.35-0.63)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard).*

[b] *The evidence was downgraded by 1 increment due to serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population).*

[c] *Confidence interval crossed the decision thresholds corresponding to 'high sensitivity' (90%) and 'low sensitivity' (60%).*

[d] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

[e] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).*

[f] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[g] *Confidence interval crossed the decision threshold corresponding to 'low specificity' (50%).*

[h] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from people taking long term topical steroids to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 5 µg ACTH test).*

[i] *The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); unclear timing between index test and reference standard and high risk of bias arising from the patient flow (missing data)).*

[j] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from tuberculosis population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml Synacthen test).*

[k] *The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; whether reference standard was conducted without knowledge of index test results; or timing between index test and reference standard).*

[l] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml ACTH test).*

Table 6: Clinical evidence summary: salt craving

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Salt intake for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.15 (0.06-0.28)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[c]	Specificity=0.76 (0.63-0.86)	VERY LOW
Salt intake for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.19 (0.11-0.30)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[c]	Specificity=0.79 (0.59-0.92)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
standard data collected cross-sectionally)							
Salt intake for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[d]	Sensitivity=0.20 (0.01-0.72)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.80 (0.71-0.87)	VERY LOW
Salt intake for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious	Not serious	Very serious[b]	Serious[d]	Sensitivity=0.17 (0.00-0.64)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.80 (0.71-0.87)	VERY LOW
Salt craving for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected tuberculosis							
1 cross-sectional study	75	Very serious[e]	Not serious	Very serious[f]	Serious[c]	Sensitivity=0.82 (0.63-0.94)	VERY LOW
		Very serious[e]	Not serious	Very serious[f]	Not serious	Specificity=0.19 (0.09-0.33)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard).*

[b] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).*

[c] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

[d] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[e] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); unclear timing between index test and reference standard and high risk of bias arising from the patient flow (missing data)).

[f] The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from tuberculosis population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml Synacthen test).

Table 7: Clinical evidence summary: weight loss

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Weight loss for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Serious[c]	Sensitivity=0.68 (0.53-0.81)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.34 (0.22-0.47)	VERY LOW
Weight loss for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Not Serious	Sensitivity=0.72 (0.60-0.81)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Serious[d]	Specificity=0.46 (0.28-0.66)	VERY LOW
Weight loss for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Very serious[e]	Sensitivity=0.80 (0.28-0.99)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.34 (0.25-0.44)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Weight loss for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV infection							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	106	Very serious[a]	Not serious	Very serious[b]	Very serious[e]	Sensitivity=0.83 (0.36-1.00)	VERY LOW
		Very serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.34 (0.25-0.44)	VERY LOW
Weight loss for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in adults with dermatological conditions using topical corticosteroids							
1 cross-sectional study	42	Very serious[a]	Not serious	Very serious[f]	Not serious	Sensitivity=0.06 (0.00-0.29)	VERY LOW
		Very serious[a]	Not serious	Very serious[f]	Not serious	Specificity=1.00 (0.86-1.00)	VERY LOW
Weight loss for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected tuberculosis							
1 cross-sectional study	75	Very serious[g]	Not serious	Very serious[h]	Not serious	Sensitivity=0.21 (0.08-0.41)	VERY LOW
		Very serious[g]	Not serious	Very serious[h]	Not serious	Specificity=0.94 (0.82-0.99)	VERY LOW
Weight loss for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS (Wolff 2021)							
1 prospective cohort study (index test and reference standard data collected cross-sectionally)	63	Very serious[i]	Not serious	Very serious[j]	Very serious[e]	Sensitivity=0.83 (0.52-0.98)	VERY LOW
		Very serious[i]	Not serious	Very serious[j]	Not serious	Specificity=0.29 (0.17-0.44)	VERY LOW

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard).

[b] The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).

[c] Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).

[d] Confidence interval crossed the decision threshold corresponding to 'low specificity' (50%).

[e] *Confidence interval crossed the decision thresholds corresponding to 'high sensitivity' (90%) and 'low sensitivity' (60%).*

[f] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from people taking long term topical steroids to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 5 µg ACTH test).*

[g] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); unclear timing between index test and reference standard and high risk of bias arising from the patient flow (missing data)).*

[h] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from tuberculosis population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml Synacthen test).*

[i] *The evidence was downgraded by 2 increments due to very high risk of bias (unclear reporting on patient selection; whether reference standard was conducted without knowledge of index test results; or timing between index test and reference standard).*

[j] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/ml ACTH test).*

Table 8: Clinical evidence summary: Hyponatraemia (serum sodium <135 mEq/L) for diagnosing adrenal insufficiency.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Hyponatraemia (<135mEq/l) for diagnosing adrenal insufficiency (basal cortisol < 9 µg/dl and/or peak cortisol < 18 µg/dl after short 250 µg Synacthen test) in people with stable liver cirrhosis							
1 cross sectional study	132	Serious[a]	Not serious	Serious[b]	Not Serious	Sensitivity=0.37 (0.27-0.48)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=0.91 (0.79-0.98)	VERY LOW
Hyponatraemia (serum Na < 135 mEq/L) for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in adults with HIV-infection							
1 prospective cohort study	106	Very Serious[c]	Not serious	Very serious[d]	Serious[e]	Sensitivity=0.51 (0.36-0.66)	VERY LOW
		Very Serious[c]	Not serious	Very serious[d]	Serious[f]	Specificity=0.64 (0.51-0.76)	VERY LOW
Hyponatraemia (serum Na < 135 mEq/L) for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in adults with HIV-infection							
1 prospective cohort study	106	Very Serious[c]	Not serious	Very serious[d]	Not serious	Sensitivity=0.46 (0.35-0.58)	VERY LOW
		Very Serious[c]	Not serious	Very serious[d]	Very serious[g]	Specificity=0.68 (0.48-0.84)	VERY LOW
Hyponatraemia (serum Na <135mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in adults with HIV-infection							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cohort study	106	Very Serious[c]	Not serious	Very serious[d]	Serious[e]	Sensitivity=0.40 (0.05-0.85)	VERY LOW
		Very Serious[c]	Not serious	Very serious[d]	Serious[h]	Specificity=0.57 (0.47-0.67)	VERY LOW
Hyponatraemia (serum Na <135 mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in adults with HIV-infection							
1 prospective cohort study	106	Very Serious[c]	Not serious	Very serious[d]	Serious[e]	Sensitivity=0.33 (0.04-0.78)	VERY LOW
		Very Serious[c]	Not serious	Very serious[d]	Serious[h]	Specificity=0.57 (0.47-0.67)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment due to high risk of bias (unclear patient selection, unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard).*

[b] *The evidence was downgraded by 1 increment due to serious indirectness (population indirectness due to concerns over applicability of evidence from stable liver cirrhosis population to general population).*

[c] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection; unclear application of the index test; unclear application of the reference standard and the timing between index test and reference standard).*

[d] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).*

[e] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[f] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

[g] *Confidence interval crossed the decision thresholds corresponding to 'high specificity' (70%) and 'low specificity' (50%).*

[h] *Confidence interval crossed the decision threshold corresponding to 'low specificity' (50%).*

Table 9: Clinical evidence summary: Hyperkalaemia (serum Potassium >5 mEq/L) for diagnosing adrenal insufficiency.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[b]	Not serious	Sensitivity=0.11 (0.04-0.23)	VERY LOW
		Very Serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.88 (0.77-0.95)	VERY LOW
Hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
	106	Very Serious[a]	Not serious	Very serious[b]	Not serious	Sensitivity=0.13 (0.06-0.22)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cohort study		Very Serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.93 (0.76-0.99)	VERY LOW
Hyperkalaemia (serum potassium <5mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[b]	Very serious[c]	Sensitivity=0.60 (0.15-0.95)	VERY LOW
		Very Serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.91 (0.84-0.96)	VERY LOW
Hyperkalaemia (serum potassium >5 mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[b]	Serious[d]	Sensitivity=0.50 (0.12-0.88)	VERY LOW
		Very Serious[a]	Not serious	Very serious[b]	Not serious	Specificity=0.91 (0.84-0.96)	VERY LOW

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection; unclear application of the index test; unclear application of the reference standard and the timing between index test and reference standard).

[b] The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).

[c] Confidence interval crossed the decision thresholds corresponding to 'high sensitivity' (90%) and 'low sensitivity' (60%).

[d] Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).

Table 10: Clinical evidence summary: nausea and vomiting for diagnosing adrenal insufficiency.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Nausea and vomiting for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in people using topical corticosteroids for at least 12 months							
1 cross sectional study	42	Very Serious[a]	Not serious	Very serious[b]	Not serious	Sensitivity=0.00 (0.00-0.20)	VERY LOW
		Very Serious[a]	Not serious	Very serious[b]	Not serious	Specificity=1.00 (0.86-1.00)	VERY LOW

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection, unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard).

[b] The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from topical steroid use population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose ACTH test).

Table 11: Clinical evidence summary: nausea for diagnosing adrenal insufficiency.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Nausea for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB							
1 cross sectional study	92 (75 analysed)	Serious[a]	Not serious	Serious[b]	Not Serious	Sensitivity=0.57 (0.37-0.76)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=0.55 (0.40-0.70)	VERY LOW
Nausea for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS							
1 prospective cohort study	72 (63 analysed)	Very Serious[c]	Not serious	Very serious[d]	Serious[e]	Sensitivity=0.50 (0.21-0.79)	VERY LOW
		Very Serious[c]	Not serious	Very serious[d]	Very serious[f]	Specificity=0.61 (0.46-0.74)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection; unclear application of the index test; unclear application of the reference standard, the timing between index test and reference standard and patient flow (17 of 92 missing data sheets).*

[b] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from suspected TB population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose ACTH test).*

[c] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection, unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard).*

[d] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/mL ACTH test).*

[e] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[f] *Confidence interval crossed the decision thresholds corresponding to 'high specificity' (70%) and 'low specificity' (50%).*

Table 12: Clinical evidence summary: vomiting for diagnosing adrenal insufficiency.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Vomiting for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB							
1 cross sectional study	92 (75 analysed)	Serious[a]	Not serious	Serious[b]	Serious[c]	Sensitivity=0.68 (0.48-0.84)	VERY LOW
		Serious[a]	Not serious	Serious[b]	Not serious	Specificity=0.26 (0.14-0.40)	VERY LOW
Vomiting for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 prospective cohort study	72 (63 analysed)	Very Serious[d]	Not serious	Very serious[e]	Serious[c]	Sensitivity=0.42 (0.15-0.72)	VERY LOW
		Very Serious[d]	Not serious	Very serious[e]	Very serious[f]	Specificity=0.69 (0.54-0.81)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection; unclear application of the index test; unclear application of the reference standard, the timing between index test and reference standard and patient flow (17 of 92 missing data sheets).*

[b] *Indirectness was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from suspected TB population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose ACTH test).*

[c] *Confidence interval crossed the decision threshold corresponding to 'low sensitivity' (60%).*

[d] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection, unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard).*

[e] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/mL ACTH test).*

[f] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

Table 13: Clinical evidence summary: Diarrhoea for diagnosing adrenal insufficiency

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Diarrhoea for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS							
1 prospective cohort study	72 (63 analysed)	Very serious[a]	Not serious	Serious[b]	Not Serious	Sensitivity=0.25 (0.05-0.57)	VERY LOW
		Very serious[a]	Not serious	Serious[b]	Serious[c]	Specificity=0.69 (0.54-0.81)	VERY LOW
Diarrhoea for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[d]	Not serious	Sensitivity=0.17 (0.08-0.31)	VERY LOW
		Very Serious[a]	Not serious	Very serious[d]	Serious[e]	Specificity=0.78 (0.65-0.88)	VERY LOW
Diarrhoea for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[d]	Not serious	Sensitivity=0.22 (0.13-0.33)	VERY LOW
		Very Serious[a]	Not serious	Very serious[d]	Very serious[e]	Specificity=0.86 (0.67-0.96)	VERY LOW

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Diarrhoea for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[d]	Not serious	Sensitivity=0.00 (0.00-0.52)	VERY LOW
		Very Serious[a]	Not serious	Very serious[d]	Not serious	Specificity=0.79 (0.70-0.87)	VERY LOW
Diarrhoea for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection							
1 prospective cohort study	106	Very Serious[a]	Not serious	Very serious[d]	Not serious	Sensitivity=0.00 (0.00-0.46)	VERY LOW
		Very Serious[a]	Not serious	Very serious[d]	Not serious	Specificity=0.79 (0.70-0.87)	VERY LOW

[a] *Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments due to very high risk of bias (unclear patient selection, unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard).*

[b] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/mL ACTH test).*

[c] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

[d] *The evidence was downgraded by 2 increments due to very serious indirectness (serious population indirectness due to concerns over applicability of evidence from HIV infection population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test).*

[e] *Confidence interval crossed the decision threshold corresponding to 'high specificity' (70%).*

See appendix F for full details of Diagnostic evidence.

1.1.7. Economic evidence

1.1.7.1. Included studies.

No health economic studies were included.

1.1.7.2. Excluded studies.

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix F.

1.1.8. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2. The committee's discussion and interpretation of the evidence

There was limited evidence for this review question, so the committee also used their clinical knowledge and experience to make the recommendations.

1.2.1. The outcomes that matter most

Signs and symptoms review

The committee considered the diagnostic measures of sensitivity and specificity for the signs and symptoms that are associated with adrenal insufficiency, or that predict its occurrence. Clinical decision thresholds were set by the committee as sensitivity/specificity=0.9 and 0.7 above which a test would be recommended and 0.6 and 0.5 below which a test is of no clinical use. The committee prioritised sensitivity over specificity because the signs and symptoms would be used to help select those suspected of having adrenal insufficiency, in whom further investigation and timely treatment may be required. As there was sufficient sensitivity and specificity data available, no association data was included in the review.

Risk factors review.

The committee considered association data (such as adjusted hazard ratios, risk ratios or odds ratios) along with diagnostic accuracy data of any risk prediction tools to identify the association and predictive accuracy of specific factors or patient characteristics that may lead to developing adrenal insufficiency. No relevant evidence was identified.

1.2.2. The quality of the evidence

Signs and symptoms review

A search was conducted for cross-sectional (single gate) studies reporting the diagnostic accuracy of signs and symptoms to identify whether adrenal insufficiency is present. Evidence was very limited, and six studies were included in the review. Evidence was identified for the following signs and symptoms: low blood pressure, hyperpigmentation, lethargy, salt craving, weight loss, hyponatraemia, hyperkalaemia, nausea, vomiting and diarrhoea. No evidence was identified for hypoglycaemia or failure to respond to initial treatments.

Evidence was from a mix of populations. Three studies were based on people with HIV/AIDS, one study was based on people with dermatological conditions using topical corticosteroids, one study was based on people with suspected tuberculosis and one study was based on people with liver cirrhosis. All studies were conducted in adults and no studies were identified for children.

A variety of reference standard tests and cut-offs were used to identify adrenal insufficiency and one study used more than one reference standard for diagnosis. The majority of studies used the Short Synacthen Test (either the standard or low dose).

All evidence was rated very low quality due to the risk of bias and imprecision around the effect estimate. Risk of bias was rated very high due to unclear recruitment strategies (whether random/consecutive), uncertainty around whether the sign/symptom was recorded without knowledge of the diagnosis and vice versa and unclear timing between the recording of the sign/symptom and the diagnosis. Many outcomes were downgraded for imprecision due to small study sizes and the confidence intervals crossing the decision thresholds, indicating conflicting interpretations of the result.

Meta-analysis of the data was not possible due to the differences in populations, reference standards and the cortisol cut-offs used, meaning that all results were based on small individual studies.

Risk factors review

A search was conducted for prospective cohort studies with multivariable analysis reporting the predictive value of risk factors for adrenal insufficiency. However, no evidence was identified so the committee used their clinical knowledge and experience to make the recommendations.

1.2.3. Benefits and harms

The committee discussed the evidence base available for the signs and symptoms review. Evidence was identified for the following signs and symptoms: low blood pressure (3 studies), hyperpigmentation (2 studies), lethargy (5 studies), salt craving (2 studies), weight loss (4 studies), hyponatraemia (2 studies), hyperkalaemia (1 study), nausea (2 studies, vomiting (2 studies), nausea and vomiting combined (1 study) and diarrhoea (2 studies). Overall, the evidence was reported in six studies. However, one study reported each sign/symptom at four different definitions of adrenal insufficiency and cut-offs so there are many more outcomes included.

The committee noted that the populations in the included studies were very specific (HIV, TB and liver cirrhosis) and were unsure how relevant the evidence was to make recommendations for a general adrenal insufficiency population.

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee set clinical decision thresholds as sensitivity/specificity 90% and 70% above which a test would be recommended and 60% and 50% below which a test is of no clinical use. Using these thresholds none of the signs and symptoms met the agreed threshold of 90% for sensitivity to base recommendations. Several outcomes reached the specificity threshold of 70% however, when looking at the paired values together, none of these reached the sensitivity threshold which was considered of higher priority in clinical decision making. The committee noted the high specificity for hyperpigmentation and discussed it is common in people with primary AI and the clearest indicator for suspecting the condition. They noted this feature may not be easily recognised in people with black or brown skin and that clinicians should inspect buccal mucosa, surgical scars and ask the person if they have noticed any change to their skin.

Other symptoms also had a high specificity, such as hyperkalaemia but the committee noted these are very uncommon. Due to the limitations of the available evidence the committee decided to use their consensus opinion to formulate recommendations and agreed on a weaker 'consider' recommendation for the specific signs and symptoms indicative of adrenal insufficiency.

The committee agreed that the symptoms and signs associated with adrenal insufficiency were common to a range of conditions and this is partly why a diagnosis of adrenal insufficiency can be missed. Nevertheless, the committee agreed that when one or more of the symptoms, signs or features are present without an alternative explanation, it should raise suspicion of adrenal insufficiency amongst clinicians. They discussed that non-specific symptoms such as lethargy or diarrhoea are too general and might lead to over-testing, therefore these symptoms would also need to be persistent and other potential causes ruled out before warranting further investigation. The committee discussed the needs of young children and people not able to communicate how they are feeling, noting that clinicians and carers need to be vigilant in monitoring for signs of adrenal insufficiency as these can be subtle and easily missed.

The committee noted that hyponatraemia, whilst common, can be indicative of adrenal insufficiency if it occurs in conjunction with other symptoms listed. Hyponatraemia can be profound in primary adrenal insufficiency and associated with significant postural symptoms due to both glucocorticoid (GC) and mineralocorticoid deficiencies.

The committee also agreed through consensus opinion that features such as hypoglycaemia, faltering growth, hypotensive crisis, and differences in sex and development in children should also prompt consideration of adrenal insufficiency, especially when these are not in isolation. For example, hypoglycaemia by itself wouldn't necessarily indicate adrenal insufficiency but if other causes have been excluded such as not being small for gestational age and other investigations as part of a hypoglycaemia screen have not shown other causes then adrenal insufficiency should be suspected, and the cortisol levels should be checked.

The committee decided to make consensus recommendations drawing on their experience of symptoms and signs seen in clinical practice, and their knowledge of the risk factors associated with medications and people with other co-existing conditions and comorbidities. The most common coexisting conditions include primary hypothyroidism and type 1 diabetes. However, clinicians should be aware that there are some rare co-exiting conditions such as Adrenoleukodystrophy and Adrenomyeloneuropathy where adrenal insufficiency should not be overlooked as investigations are often focussed on the conditions themselves and adrenal insufficiency is missed.

1.2.4. Cost-effectiveness and resource use

No economic evaluations were identified for this review question. Due to a lack of clinical evidence that was generalisable to all people with adrenal insufficiency, the committee made consensus recommendations that were reflective of current practice. These recommendations are therefore not expected to result in a significant resource impact.

1.2.5. Recommendations supported by this evidence review.

This evidence review supports recommendations 1.2.1 to 1.2.4 and 1.9.6 to 1.9.7.

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Appendices

Appendix A Review protocols

A.1 Review protocol for when to suspect adrenal crisis.

ID	Field	Content
1.	Review title	2.1 When to suspect adrenal insufficiency
2.	Review question	When should adrenal insufficiency be suspected (for example, based on risk factors or symptoms)?
3.	Objective	To identify people who are at risk of adrenal insufficiency through risk factors or symptoms that are either strongly associated with AI or that predict its occurrence. This review will be conducted in 2 parts: 1) Signs and symptoms: this part will aim to identify the association of specific signs or symptoms that are indicative of having AI (diagnostic association) 2) Risk factors: this part will aim to identify the association and predictive accuracy of specific factors or patient characteristics that may lead to developing AI in the future (prognostic factor association)
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies

		Any search filters applied (e.g. study design) will be found in the review appendix. The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	Inclusion: Adults and children without a diagnosis of adrenal insufficiency Exclusion: None identified
7.	Exposure	**Signs/symptoms:** • Low blood pressure (hypotension including postural hypotension) • Hyperpigmentation • Lethargy • Salt craving • Weight loss • Hyponatraemia • Hyperkalaemia • Hypoglycaemia • Nausea • vomiting • Diarrhoea

		• Failure to respond to initial treatments. **Risk factors:** <u>Drugs:</u> • checkpoint inhibitors e.g., atezolizumab, avelumab, durvalumab • opioids • glucocorticoid therapy (any route) • adrenal enzyme inhibitors: e.g. mitotane ketoconazole, itraconazole, voriconazole, metyrapone, etomidate, aminoglutethimidie, phenobarbital, phenytoin, rifampicin • mifepristone • chlorpromazine • imipramine <u>Co-existing conditions or co-morbidities:</u> • Primary hypothyroidism • Type 1 diabetes • Premature ovarian insufficiency • Autoimmune Polyendocrinopathy Syndrome type 1 • Pituitary tumours • Hypothalamic tumours or disease • Traumatic brain injury (particularly base of skull fracture) • Infections: TB, HIV/AIDS, CMV, fungal infections, syphilis, Lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis Specific to children and neonates: • Prolonged jaundice • Hypoglycaemia

		• Ambiguous genitalia (in females) • Hypotensive crisis Any of the above, alone or in combination
8.	Reference standard/Confounding factors	**Reference standard for signs and symptoms review:** • Clinical diagnosis of adrenal insufficiency by a specialist **Confounding factors for risk factors review:** • Any exposure/risk factors listed above. • Age and sex as a minimum.
9.	Types of study to be included	**For signs and symptoms review:** • Cross sectional (single gate) diagnostic studies • If no or insufficient diagnostic accuracy studies are identified, prospective cohort studies looking at the association between individual or combinations of signs and symptoms (multivariable models/algorithms) and a confirmed diagnosis of adrenal insufficiency. • Systematic reviews of the above **For risk factor review:** • Prospective cohort studies with multivariate analysis. • Systematic reviews of the above. Studies will only be included if key confounders have been accounted for in a multivariate analysis. Key confounders will vary based on each risk factor but should at least include age and sex. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Retrospective cohort studies case-control (two-gate) diagnostic studies Before and after studies

		Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	

12.	Primary outcomes (critical outcomes)	**For signs and symptoms review:**
		• Diagnostic accuracy data
		  ○ Sensitivity (prioritised)
		  ○ specificity
		If no sensitivity or specificity, LR- and LR+ if raw data unavailable and unable to calculate from 2 x 2 table.
		Diagnostic association of signs and symptoms with a confirmed diagnosis of adrenal insufficiency. Measured by:
		• Association data
		  ○ Adjusted hazard ratios, odds ratios or risk ratios.
		• Discrimination
		  ○ For example, C statistic, area under ROC curve
		• Calibration
		  ○ For example, calibration slope
		For risk factors review:
		• Diagnosis of adrenal insufficiency as defined by authors and reported as adjusted hazard ratios, odds ratios or risk ratios.
		• For risk prediction tools: sensitivity, specificity and statistical measures of discrimination and calibration including Area Under the Curve (AUC) for risk tools.

13.	Data extraction (selection and coding)	EndNote will be used for reference management, citations and bibliographies. All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

		The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately. • a sample of the data extractions • correct methods are used to synthesise data. • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. These may include: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Nonrandomised study, including cohort studies: Cochrane ROBINS-I • Clinical prediction study (risk prediction modelling) for a prognosis or diagnosis: PROBAST • Risk factors study: QUIPs • Diagnostic association: QUADAS
15.	Strategy for data synthesis	Where possible data from diagnostic studies will be meta-analysed using Cochrane Review Manager (RevMan5) (if at least 3 studies reporting data at the same diagnostic threshold). Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Where association data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.		
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: None identified		
17.	Type and method of review	☐	Intervention	
		☒	Diagnostic	
		☒	Prognostic	
		☐	Qualitative	
		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	February 2023		
21.	Anticipated completion date	-		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐

		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail Hypoadrenalism@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer] Madelaine Zucker [Technical analyst] Alexandra Bannon [Health economist] Stephen Deed [Information specialist		
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's		

		declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10237.	
28.	Other registration details		
29.	Reference/URL for published protocol		
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords		
32.	Details of existing review of same topic by same authors		
33.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	-	

35.	Details of final publication	www.nice.org.uk

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[6] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of

	applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2007 will be rated as 'Not applicable'. • Studies published before 2007 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[6]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 14: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Observational studies Systematic review studies Prognostic studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Observational studies Systematic review studies Prognostic studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 9 of 12, 26 September 2023	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 September 2023	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or

	hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	exp Hypotension/
36.	("low blood pressure" or hypotension or "hypotensive crisis").ti,ab,kf.
37.	Hyperpigmentation/
38.	(hyperpigmentation or pigmentation).ti,ab,kf.
39.	Lethargy/
40.	lethargy.ti,ab,kf.
41.	(salt* adj3 crav*).ti,ab,kf.
42.	Weight Loss/ or Emaciation/
43.	(weight adj2 (loss or losing or decreas*)).ti,ab,kf.
44.	emaciat*.ti,ab,kf.
45.	Hyponatremia/

46.	(hyponatraemia or hyponatremia).ti,ab,kf.
47.	(low adj3 (sodium or salt)).ti,ab,kf.
48.	Hyperkalemia/
49.	(hyperkalaemia or hyperkalemia).ti,ab,kf.
50.	(high adj3 potassium).ti,ab,kf.
51.	Hypoglycemia/
52.	(hypoglycaemia or hypoglycemia).ti,ab,kf.
53.	(low adj3 ("blood glucose" or "blood sugar")).ti,ab,kf.
54.	Nausea/
55.	nausea.ti,ab,kf.
56.	Vomiting/
57.	(vomit* or emesis).ti,ab,kf.
58.	exp Diarrhea/
59.	(diarrhoea or diarrhea).ti,ab,kf.
60.	(fail* adj3 respon* adj3 (initial or treatment*)).ti,ab,kf.
61.	Immune Checkpoint Inhibitors/
62.	"checkpoint inhibitor*".ti,ab,kf.
63.	(atezolizumab or avelumab or durvalumab).ti,ab,kf.
64.	exp Analgesics, Opioid/
65.	opioid*.ti,ab,kf.
66.	exp Glucocorticoids/ or Steroids/ or exp Corticosterone/ or Cortisone/ or Hydrocortisone/
67.	(glucocorticoid* or glucocorticosteroid* or steroid* or corticosterone* or cortisone* or hydrocortisone*).ti,ab,kf.
68.	Enzyme Inhibitors/
69.	"enzyme inhibitor*".ti,ab,kf.
70.	Mitotane/ or Ketoconazole/ or Itraconazole/ or Voriconazole/ or Metyrapone/ or Etomidate/ or Aminoglutethimide/ or exp Phenobarbital/ or Phenytoin/ or Rifampin/
71.	(mitotane or ketoconazole or itraconazole or voriconazole or metyrapone or etomidate or aminoglutethimide or phenobarbital or phenytoin or rifampicin).ti,ab,kf.
72.	Mifepristone/
73.	mifepristone.ti,ab,kf.
74.	Chlorpromazine/
75.	chlorpromazine.ti,ab,kf.
76.	Imipramine/
77.	imipramine.ti,ab,kf.
78.	Primary Ovarian Insufficiency/
79.	((primary or premature) adj2 ovarian adj2 (insufficien* or fail*)).ti,ab,kf.
80.	Hypothalamo-Hypophyseal System/ and Pituitary-Adrenal System/
81.	((HPA or "hypothalamo-pituitary-adrenal") adj3 "suppress*").ti,ab,kf.
82.	((hypothalam* or pituitary) adj3 (disease* or disorder* or neoplasm* or tumour* or tumor* or adenoma*)).ti,ab,kf.
83.	Hypothyroidism/
84.	"primary hypothyroidism".ti,ab,kf.
85.	Brain Neoplasms/
86.	(brain adj3 (neoplasm* or tumour* or tumor* or adenoma*)).ti,ab,kf.
87.	(glioma* or meningioma* or schwannoma*).ti,ab,kf.
88.	Polyendocrinopathies, Autoimmune/

89.	((autoimmune or "auto immune") adj3 (polyglandular or "poly glandular" or polyendocrin* or "poly endocrin*")).ti,ab,kf.
90.	("APS Type*" or APS1 or APS2 or "APS-1" or "APS-2").ti,ab,kf.
91.	Diabetes Mellitus, Type 1/
92.	((autoimmune or "auto immune" or "type 1" or "type i" or type1 or typei or "insulin dependent") adj3 diabetes).ti,ab,kf.
93.	exp Brain Injuries, Traumatic/ or exp Skull Fractures/
94.	(brain adj2 (trauma* or injur*)).ti,ab,kf.
95.	(skull adj2 fracture*).ti,ab,kf.
96.	exp Tuberculosis/
97.	tuberculosis.ti,ab,kf.
98.	exp HIV/
99.	(HIV or "human immunodeficiency virus" or "human immuno deficiency virus" or "human immune deficiency virus").ti,ab,kf.
100.	Acquired Immunodeficiency Syndrome/
101.	(AIDS or "acquired immune deficiency syndrome*" or "acquired immuno deficiency syndrome*" or "acquired immunodeficiency syndrome*").ti,ab,kf.
102.	exp Cytomegalovirus Infections/
103.	(CMV or cytomegalovirus).ti,ab,kf.
104.	exp Mycoses/
105.	((fungal adj3 (infection* or disease*)) or mycoses or mycosis).ti,ab,kf.
106.	Toxoplasmosis/ or Histoplasmosis/ or Coccidioidomycosis/
107.	(toxoplasmos* or histoplasmos* or coccidioidomycos*).ti,ab,kf.
108.	exp Syphilis/
109.	syphilis.ti,ab,kf.
110.	exp Hypophysitis/
111.	((lymphocytic or autoimmune or " auto immune") adj3 hypophysitis).ti,ab,kf.
112.	exp Sarcoidosis/
113.	sarcoidosis.ti,ab,kf.
114.	Histiocytosis, Langerhans-Cell/
115.	(histiocytosis adj2 (X or langerhans)).ti,ab,kf.
116.	Hemochromatosis/
117.	(hemochromatosis or haemochromatosis).ti,ab,kf.
118.	exp Jaundice/
119.	jaundice*.ti,ab,kf.
120.	"Disorders of Sex Development"/
121.	"ambiguous genital*".ti,ab,kf.
122.	(symptom* or suspect* or suspicion).ti,ab.
123.	or/35-122
124.	34 and 123
125.	Epidemiologic studies/
126.	Observational study/
127.	exp Cohort studies/
128.	(cohort adj (study or studies or analys* or data)).ti,ab.
129.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
130.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.

131.	Controlled Before-After Studies/
132.	Historically Controlled Study/
133.	Interrupted Time Series Analysis/
134.	(before adj2 after adj2 (study or studies or data)).ti,ab.
135.	exp case control study/
136.	case control*.ti,ab.
137.	Cross-sectional studies/
138.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
139.	or/125-138
140.	Meta-Analysis/
141.	Meta-Analysis as Topic/
142.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
143.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
144.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
145.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
146.	(search* adj4 literature).ab.
147.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
148.	cochrane.jw.
149.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
150.	or/140-149
151.	exp Prognosis/
152.	Disease progression/
153.	(prognos* or predict*).ti,ab.
154.	(validat* or rule*).ti,ab.
155.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif*)).ti,ab.
156.	(decision* and (model* or clinical*)).ti,ab.
157.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
158.	ROC curve/
159.	or/151-158
160.	124 and (139 or 150 or 159)

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.

6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	*hypotension/
35.	("low blood pressure" or hypotension or "hypotensive crisis").ti,ab,kf.
36.	*hyperpigmentation/
37.	(hyperpigmentation or pigmentation).ti,ab,kf.
38.	*lethargy/
39.	lethargy.ti,ab,kf.
40.	(salt* adj3 crav*).ti,ab,kf.
41.	exp *body weight loss/
42.	(weight adj2 (loss or losing or decreas*)).ti,ab,kf.
43.	emaciat*.ti,ab,kf.
44.	*hyponatremia/
45.	(hyponatraemia or hyponatremia).ti,ab,kf.
46.	(low adj3 (sodium or salt)).ti,ab,kf.
47.	*hyperkalemia/
48.	(hyperkalaemia or hyperkalemia).ti,ab,kf.
49.	(high adj3 potassium).ti,ab,kf.

50.	*hypoglycemia/
51.	(hypoglycaemia or hypoglycemia).ti,ab,kf.
52.	(low adj3 ("blood glucose" or "blood sugar")).ti,ab,kf.
53.	*nausea/
54.	nausea.ti,ab,kf.
55.	*vomiting/
56.	(vomit* or emesis).ti,ab,kf.
57.	*diarrhea/
58.	(diarrhoea or diarrhea).ti,ab,kf.
59.	*treatment failure/
60.	(fail* adj3 respon* adj3 (initial or treatment*)).ti,ab,kf.
61.	*immune checkpoint inhibitor/
62.	"checkpoint inhibitor*".ti,ab,kf.
63.	*atezolizumab/ or *avelumab/ or *durvalumab/
64.	(atezolizumab or avelumab or durvalumab).ti,ab,kf.
65.	*opiate/
66.	opioid*.ti,ab,kf.
67.	*glucocorticoid/ or *steroid/ or *corticosterone/ or *cortisone/ or *hydrocortisone/
68.	(glucocorticoid* or glucocorticosteroid* or steroid* or corticosterone* or cortisone* or hydrocortisone*).ti,ab,kf.
69.	*enzyme inhibitor/
70.	"enzyme inhibitor*".ti,ab,kf.
71.	*mitotane/ or *ketoconazole/ or *itraconazole/ or *voriconazole/ or *metyrapone/ or *etomidate/ or *aminoglutethimide/ or *phenobarbital/ or *phenytoin/ or *rifampin/
72.	(mitotane or ketoconazole or itraconazole or voriconazole or metyrapone or etomidate or aminoglutethimide or phenobarbital or phenytoin or rifampicin).ti,ab,kf.
73.	*mifepristone/
74.	mifepristone.ti,ab,kf.
75.	*chlorpromazine/
76.	chlorpromazine.ti,ab,kf.
77.	*imipramine/
78.	imipramine.ti,ab,kf.
79.	*premature ovarian failure/
80.	((primary or premature) adj2 ovarian adj2 (insufficien* or fail*)).ti,ab,kf.
81.	*hypothalamus hypophysis adrenal system/
82.	((HPA or "hypothalamo-pituitary-adrenal") adj3 "suppress*").ti,ab,kf.
83.	((hypothalam* or pituitary) adj3 (disease* or disorder* or neoplasm* or tumour* or tumor* or adenoma*)).ti,ab,kf.
84.	*hypothyroidism/
85.	"primary hypothyroidism".ti,ab,kf.
86.	*brain tumor/
87.	(brain adj3 (neoplasm* or tumour* or tumor* or adenoma*)).ti,ab,kf.
88.	(glioma* or meningioma* or schwannoma*).ti,ab,kf.
89.	*polyendocrinopathy/
90.	((autoimmune or "auto immune") adj3 (polyglandular or "poly glandular" or polyendocrin* or "poly endocrin*")).ti,ab,kf.
91.	("APS Type*" or APS1 or APS2 or "APS-1" or "APS-2").ti,ab,kf.
92.	exp *insulin dependent diabetes mellitus/

93.	((autoimmune or "auto immune" or "type 1" or "type i" or type1 or typei or "insulin dependent") adj3 diabetes).ti,ab,kf.
94.	*traumatic brain injury/ or *skull base fracture/
95.	(brain adj2 (trauma* or injur*)).ti,ab,kf.
96.	(skull adj2 fracture*).ti,ab,kf.
97.	*tuberculosis/
98.	tuberculosis.ti,ab,kf.
99.	*Human immunodeficiency virus/
100.	(HIV or "human immunodeficiency virus" or "human immuno deficiency virus" or "human immune deficiency virus").ti,ab,kf.
101.	*acquired immune deficiency syndrome/
102.	(AIDS or "acquired immune deficiency syndrome*" or "acquired immuno deficiency syndrome*" or "acquired immunodeficiency syndrome*").ti,ab,kf.
103.	exp *cytomegalovirus infection/
104.	(CMV or cytomegalovirus).ti,ab,kf.
105.	*mycosis/
106.	((fungal adj3 (infection* or disease*)) or mycoses or mycosis).ti,ab,kf.
107.	*toxoplasmosis/ or *histoplasmosis/ or *coccidioidomycosis/
108.	(toxoplasmos* or histoplasmos* or coccidioidomycos*).ti,ab,kf.
109.	*syphilis/
110.	syphilis.ti,ab,kf.
111.	exp *hypophysitis/
112.	((lymphocytic or autoimmune or " auto immune") adj3 hypophysitis).ti,ab,kf.
113.	exp *sarcoidosis/
114.	sarcoidosis.ti,ab,kf.
115.	*Langerhans cell histiocytosis/
116.	(histiocytosis adj2 (X or langerhans)).ti,ab,kf.
117.	*hemochromatosis/
118.	(hemochromatosis or haemochromatosis).ti,ab,kf.
119.	*jaundice/
120.	jaundice*.ti,ab,kf.
121.	*ambiguous genitalia/
122.	"ambiguous genital*".ti,ab,kf.
123.	(symptom* or suspect* or suspicion).ti,ab.
124.	or/34-123
125.	33 and 124
126.	Clinical study/
127.	Observational study/
128.	Family study/
129.	Longitudinal study/
130.	Retrospective study/
131.	Prospective study/
132.	Cohort analysis/
133.	Follow-up/
134.	cohort*.ti,ab.
135.	133 and 134
136.	(cohort adj (study or studies or analys* or data)).ti,ab.

137.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
138.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
139.	(before adj2 after adj2 (study or studies or data)).ti,ab.
140.	exp case control study/
141.	case control*.ti,ab.
142.	cross-sectional study/
143.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
144.	or/126-132,135-143
145.	Systematic Review/
146.	Meta-Analysis/
147.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
148.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
149.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
150.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
151.	(search* adj4 literature).ab.
152.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
153.	cochrane.jw.
154.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
155.	or/145-154
156.	prognosis/
157.	disease exacerbation/
158.	(prognos* or predict*).ti,ab.
159.	(validat* or rule*).ti,ab.
160.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif*)).ti,ab.
161.	(decision* and (model* or clinical*)).ti,ab.
162.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
163.	ROC curve/
164.	or/156-163
165.	125 and (144 or 155 or 164)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Adrenal Insufficiency] explode all trees
#2.	MeSH descriptor: [Adrenal Hyperplasia, Congenital] this term only
#3.	((addison* NEXT disease) or addisonian*):ti,ab,kw
#4.	((adrenal* or adrenocort* or adreno-cort*) near/3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)):ti,ab,kw
#5.	((cortisol or aldosterone or adrenocorticotrop* or adreno-corticotrop* or ACTH or (corticotropi* NEXT releas*) or (corticotrophi* NEXT releas*) or corticoliberin or CRH) near/3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)):ti,ab,kw

#6.	(hypoadrenal* or hypo-adrenal* or hypoadrenocorticism or "hypo adrenocorticism" or adrenoleukodystrophy or "adreno leukodystrophy" or adrenomyeloneuropathy or "adreno myeloneuropathy" or hypoaldosteronism or "hypo aldosteronism"):ti,ab,kw
#7.	((adrenogenital or "adreno genital") near/1 (syndrome or disorder*)):ti,ab,kw
#8.	((haemorrhag* or hemorrhag* or bleed*) near/3 adrenal*):ti,ab,kw
#9.	((Bronze NEXT Schilder*) or "Melanodermic Leukodystrophy" or (Schilder NEXT Addison*) or (Siemerling NEXT Creutzfeldt*)):ti,ab,kw
#10.	((Allgrove or 3A or TripleA or AAA) near/1 syndrome):ti,ab,kw
#11.	(CAH or "X-ALD"):ti,ab
#12.	((Waterhouse NEXT Friderichsen*) or "antiphospholipid syndrome"):ti,ab,kw
#13.	"Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy":ti,ab,kw
#14.	(or #1-#13)
#15.	MeSH descriptor: [Hypotension] explode all trees
#16.	("low blood pressure" or hypotension or "hypotensive crisis"):ti,ab,kw
#17.	MeSH descriptor: [Hyperpigmentation] this term only
#18.	(hyperpigmentation or pigmentation):ti,ab,kw
#19.	MeSH descriptor: [Lethargy] this term only
#20.	lethargy:ti,ab,kw
#21.	(salt* near/3 crav*):ti,ab,kw
#22.	MeSH descriptor: [Weight Loss] this term only
#23.	MeSH descriptor: [Emaciation] this term only
#24.	(weight near/2 (loss or losing or decreas*)):ti,ab,kw
#25.	emaciat*:ti,ab,kw
#26.	MeSH descriptor: [Hyponatremia] this term only
#27.	(hyponatraemia or hyponatremia):ti,ab,kw
#28.	(low near/3 (sodium or salt)):ti,ab,kw
#29.	MeSH descriptor: [Hyperkalemia] this term only
#30.	(hyperkalaemia or hyperkalemia):ti,ab,kw
#31.	(high near/3 potassium):ti,ab,kw
#32.	MeSH descriptor: [Hypoglycemia] this term only
#33.	(hypoglycaemia or hypoglycemia):ti,ab,kw
#34.	(low near/3 ("blood glucose" or "blood sugar")):ti,ab,kw
#35.	MeSH descriptor: [Nausea] this term only
#36.	nausea:ti,ab,kw
#37.	MeSH descriptor: [Vomiting] this term only
#38.	(vomit* or emesis):ti,ab,kw
#39.	MeSH descriptor: [Diarrhea] explode all trees
#40.	(diarrhoea or diarrhea):ti,ab,kw
#41.	(fail* near/3 respon* near/3 (initial or treatment*)):ti,ab,kw
#42.	MeSH descriptor: [Immune Checkpoint Inhibitors] this term only
#43.	checkpoint-inhibitor*:ti,ab,kw
#44.	(atezolizumab or avelumab or durvalumab):ti,ab,kw
#45.	MeSH descriptor: [Analgesics, Opioid] explode all trees
#46.	opioid*:ti,ab,kw
#47.	MeSH descriptor: [Glucocorticoids] explode all trees
#48.	MeSH descriptor: [Steroids] this term only
#49.	MeSH descriptor: [Corticosterone] explode all trees
#50.	MeSH descriptor: [Cortisone] this term only

#51.	MeSH descriptor: [Hydrocortisone] this term only
#52.	(glucocorticoid* or glucocorticosteroid* or steroid* or corticosterone* or cortisone* or hydrocortisone*):ti,ab,kw
#53.	MeSH descriptor: [Enzyme Inhibitors] this term only
#54.	enzyme-inhibitor*:ti,ab,kw
#55.	MeSH descriptor: [Mitotane] this term only
#56.	MeSH descriptor: [Ketoconazole] this term only
#57.	MeSH descriptor: [Itraconazole] this term only
#58.	MeSH descriptor: [Voriconazole] this term only
#59.	MeSH descriptor: [Metyrapone] this term only
#60.	MeSH descriptor: [Etomidate] this term only
#61.	MeSH descriptor: [Aminoglutethimide] this term only
#62.	MeSH descriptor: [Phenobarbital] explode all trees
#63.	MeSH descriptor: [Phenytoin] this term only
#64.	MeSH descriptor: [Rifampin] this term only
#65.	(mitotane or ketoconazole or itraconazole or voriconazole or metyrapone or etomidate or aminoglutethimide or phenobarbital or phenytoin or rifampicin):ti,ab,kw
#66.	MeSH descriptor: [Mifepristone] this term only
#67.	mifepristone:ti,ab,kw
#68.	MeSH descriptor: [Chlorpromazine] this term only
#69.	chlorpromazine:ti,ab,kw
#70.	MeSH descriptor: [Imipramine] this term only
#71.	imipramine:ti,ab,kw
#72.	MeSH descriptor: [Primary Ovarian Insufficiency] this term only
#73.	((primary or premature) near/2 ovarian near/2 (insufficien* or fail*)):ti,ab,kw
#74.	MeSH descriptor: [Hypothalamo-Hypophyseal System] this term only
#75.	MeSH descriptor: [Pituitary-Adrenal System] this term only
#76.	#74 and #75
#77.	((HPA or "hypothalamo-pituitary-adrenal") near/3 suppress*):ti,ab,kw
#78.	((hypothalam* or pituitary) near/3 (disease* or disorder* or neoplasm* or tumour* or tumor* or adenoma*)):ti,ab,kw
#79.	MeSH descriptor: [Hypothyroidism] this term only
#80.	primary hypothyroidism:ti,ab,kw
#81.	MeSH descriptor: [Brain Neoplasms] this term only
#82.	(brain near/3 (neoplasm* or tumour* or tumor* or adenoma*)):ti,ab,kw
#83.	(glioma* or meningioma* or schwannoma*):ti,ab,kw
#84.	MeSH descriptor: [Polyendocrinopathies, Autoimmune] this term only
#85.	((autoimmune or "auto immune") near/3 (polyglandular or "poly glandular" or polyendocrin* or poly-endocrin*)):ti,ab,kw
#86.	(APS-Type* or APS1 or APS2 or "APS-1" or "APS-2"):ti,ab,kw
#87.	MeSH descriptor: [Diabetes Mellitus, Type 1] this term only
#88.	((autoimmune or "auto immune" or "type 1" or "type i" or type1 or typei or "insulin dependent") near/3 diabetes):ti,ab,kw
#89.	MeSH descriptor: [Brain Injuries, Traumatic] explode all trees
#90.	MeSH descriptor: [Skull Fractures] explode all trees
#91.	(brain near/2 (trauma* or injur*)):ti,ab,kw
#92.	(skull near/2 fracture*):ti,ab,kw
#93.	MeSH descriptor: [Tuberculosis] explode all trees

#94.	tuberculosis:ti,ab,kw
#95.	MeSH descriptor: [HIV] explode all trees
#96.	(HIV or "human immunodeficiency virus" or "human immuno deficiency virus" or "human immune deficiency virus"):ti,ab,kw
#97.	MeSH descriptor: [Acquired Immunodeficiency Syndrome] this term only
#98.	(AIDS or "acquired immune deficiency syndrome" or "acquired immuno deficiency syndrome" or "acquired immunodeficiency syndrome"):ti,ab,kw
#99.	MeSH descriptor: [Cytomegalovirus Infections] explode all trees
#100.	(CMV or cytomegalovirus):ti,ab,kw
#101.	MeSH descriptor: [Mycoses] explode all trees
#102.	((fungal near/3 (infection* or disease*)) or mycoses or mycosis):ti,ab,kw
#103.	MeSH descriptor: [Toxoplasmosis] this term only
#104.	MeSH descriptor: [Histoplasmosis] this term only
#105.	MeSH descriptor: [Coccidioidomycosis] this term only
#106.	(toxoplasmos* or histoplasmos* or coccidioidomycos*):ti,ab,kw
#107.	MeSH descriptor: [Syphilis] explode all trees
#108.	syphilis:ti,ab,kw
#109.	MeSH descriptor: [Hypophysitis] explode all trees
#110.	((lymphocytic or autoimmune or " auto immune") near/3 hypophysitis):ti,ab,kw
#111.	MeSH descriptor: [Sarcoidosis] explode all trees
#112.	sarcoidosis:ti,ab,kw
#113.	MeSH descriptor: [Histiocytosis, Langerhans-Cell] this term only
#114.	(histiocytosis near/2 (X or langerhans)):ti,ab,kw
#115.	MeSH descriptor: [Hemochromatosis] this term only
#116.	(hemochromatosis or haemochromatosis):ti,ab,kw
#117.	MeSH descriptor: [Jaundice] explode all trees
#118.	jaundice*:ti,ab,kw
#119.	MeSH descriptor: [Disorders of Sex Development] this term only
#120.	ambiguous-genital*:ti,ab,kw
#121.	(symptom* or suspect* or suspicion):ti,ab
#122.	(or #15-#73)
#123.	(or #76-#121)
#124.	#122 or #123
#125.	#14 and #124
#126.	conference:pt or (clinicaltrials or trialsearch):so
#127.	#125 not #126

Epistemonikos search terms

1.	(title:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism") OR abstract:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR

	"hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism")) AND (title:("low blood pressure" OR hypotension OR "hypotensive crisis" OR hyperpigmentation OR pigmentation OR lethargy OR "salt craving" OR "weight loss" OR emaciat* OR hyponatraemia OR hyponatremia OR "low sodium" OR "low salt" OR hyperkalaemia OR hyperkalemia OR "high potassium" OR hypoglycaemia OR hypoglycemia OR "low blood glucose" OR "low blood sugar" OR nausea OR vomit* OR emesis OR diarrhoea OR diarrhea OR "checkpoint inhibitor" OR atezolizumab OR avelumab OR durvalumab OR opioid* OR glucocorticoid* OR glucocorticosteroid* OR steroid* OR corticosterone* OR cortisone* OR hydrocortisone* OR "enzyme inhibitor" OR mitotane OR ketoconazole OR itraconazole OR voriconazole OR metyrapone OR etomidate OR aminoglutethimide OR phenobarbital OR phenytoin OR rifampicin OR mifepristone OR chlorpromazine OR imipramine OR "primary ovarian insufficiency" OR "premature ovarian failure" OR "primary hypothyroidism" OR "brain tumour" OR "brain tumor" OR glioma* OR meningioma* OR schwannoma* OR "autoimmune polyglandular" OR "type 1 diabetes" OR "autoimmune diabetes" OR "brain injury" OR "brain injuries" OR "skull fracture" OR "skull fractures" OR tuberculosis OR HIV OR "human immunodeficiency virus" OR "human immuno deficiency virus" OR "human immune deficiency virus" OR AIDS OR "acquired immune deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immunodeficiency syndrome" OR cytomegalovirus OR "fungal infection" OR "fungal infections" OR mycoses OR mycosis OR toxoplasmos* OR histoplasmos* OR coccidioidomycos* OR syphilis OR "lymphocytic hypophysitis" OR sarcoidosis OR "histiocytosis X" OR langerhans OR hemochromatosis OR haemochromatosis OR jaundice* OR "ambiguous genitalia" OR "ambiguous genitals") OR abstract:("low blood pressure" OR hypotension OR "hypotensive crisis" OR hyperpigmentation OR pigmentation OR lethargy OR "salt craving" OR "weight loss" OR emaciat* OR hyponatraemia OR hyponatremia OR "low sodium" OR "low salt" OR hyperkalaemia OR hyperkalemia OR "high potassium" OR hypoglycaemia OR hypoglycemia OR "low blood glucose" OR "low blood sugar" OR nausea OR vomit* OR emesis OR diarrhoea OR diarrhea OR "checkpoint inhibitor" OR atezolizumab OR avelumab OR durvalumab OR opioid* OR glucocorticoid* OR glucocorticosteroid* OR steroid* OR corticosterone* OR cortisone* OR hydrocortisone* OR "enzyme inhibitor" OR mitotane OR ketoconazole OR itraconazole OR voriconazole OR metyrapone OR etomidate OR aminoglutethimide OR phenobarbital OR phenytoin OR rifampicin OR mifepristone OR chlorpromazine OR imipramine OR "primary ovarian insufficiency" OR "premature ovarian failure" OR "primary hypothyroidism" OR "brain tumour" OR "brain tumor" OR glioma* OR meningioma* OR schwannoma* OR "autoimmune polyglandular" OR "type 1 diabetes" OR "autoimmune diabetes" OR "brain injury" OR "brain injuries" OR "skull fracture" OR "skull fractures" OR tuberculosis OR HIV OR "human immunodeficiency virus" OR "human immuno deficiency virus" OR "human immune deficiency virus" OR AIDS OR "acquired immune deficiency syndrome" OR "acquired immuno deficiency syndrome" OR "acquired immunodeficiency syndrome" OR cytomegalovirus OR "fungal infection" OR "fungal infections" OR mycoses OR mycosis OR toxoplasmos* OR histoplasmos* OR coccidioidomycos* OR syphilis OR "lymphocytic hypophysitis" OR sarcoidosis OR "histiocytosis X" OR langerhans OR hemochromatosis OR haemochromatosis OR jaundice* OR "ambiguous genitalia" OR "ambiguous genitals"))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Adrenal Insufficiency population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards.

Table 15: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.

10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Economics/
36.	Value of life/
37.	exp "Costs and Cost Analysis"/
38.	exp Economics, Hospital/
39.	exp Economics, Medical/
40.	Economics, Nursing/
41.	Economics, Pharmaceutical/
42.	exp "Fees and Charges"/
43.	exp Budgets/
44.	budget*.ti,ab.
45.	cost*.ti.
46.	(economic* or pharmaco?economic*).ti.
47.	(price* or pricing*).ti,ab.
48.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
49.	(financ* or fee or fees).ti,ab.
50.	(value adj2 (money or monetary)).ti,ab.
51.	or/35-50

52.	34 and 51
53.	limit 52 to yr="2014 -Current"

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	health economics/

35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47
49.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

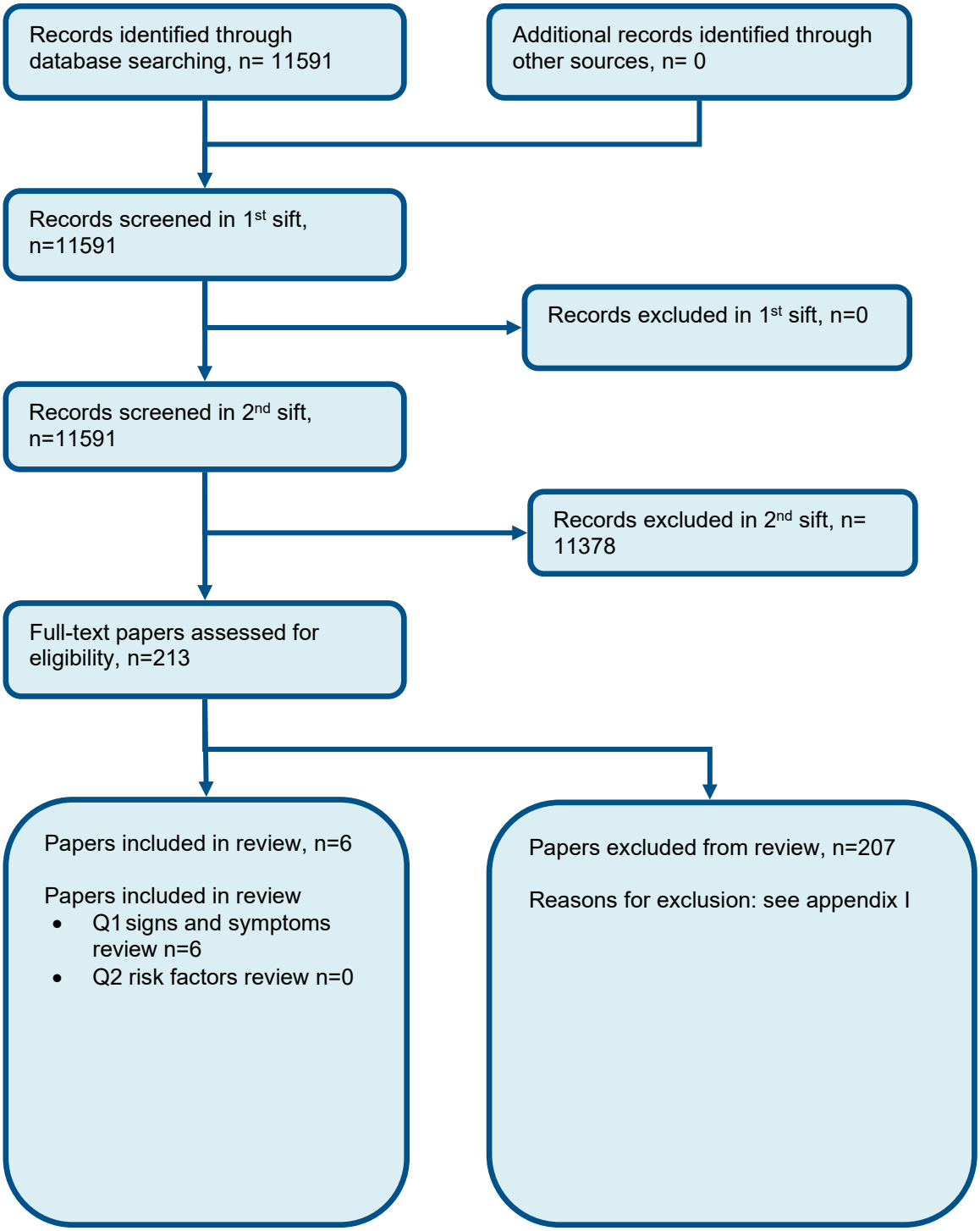
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed)
#5.	(cortisol or aldosterone or adrenocortical or adrenocorticotropi* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) AND (insufficien* or inadequac* or deficien* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or produc* or limited)
#6.	(hypoadrenalism or hypoadrenocorticism or adrenoleukodystrophy or adrenomyeloneuropathy or hypoaldosteronism)
#7.	((Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease))
#8.	(Allgrove or 3A or TripleA or AAA) AND (syndrome)
#9.	(X-ALD)
#10.	((Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome))
#11.	((Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy))
#12.	(adrenogenital or adreno genital) AND (syndrome)
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

INAHTA search terms

1.	(("Adrenal Insufficiency"[mhe]) OR (hypoadrenalism) OR (addison*) OR (adrenal insufficiency) OR (adrenal crisis))

Appendix C Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of when to suspect adrenal insufficiency



Appendix D Diagnostic evidence

Reference	**Abbott 1995[1]**
Study type	Cross-sectional
Study methodology	Data source: HIV-positive inpatients and outpatients Recruitment: recruited from the Department of Infectious Diseases (Monsall Unit Manchester, U.K.) from November 1992 to May 1993
Number of patients	Total n = 49 (impaired/abnormal rapid ACTH stimulation test n = 14, normal rapid ACTH test n = 35)
Patient characteristics	Age, median (range): 36 (25-56) years Gender (male to female ratio): 42:7 Ethnicity: not reported Setting: Department of Infectious Diseases, single centre Country: UK Inclusion criteria: HIV-positive inpatients and outpatients with CD4 counts ≤ 50 x 10^6/l Exclusion criteria: taking systemic steroids (except megestrol acetate)
Target condition(s)	Cortisol deficiency
Index test(s) and reference standard	Index tests Fatigue: subjects filled in a questionnaire to assess fatigue (graded 0 = no fatigue, 1 = occasional and mild, 2=frequent and affecting function, 3=debilitating, house-bound, 4 = severe, bed-bound) Systolic postural drop (≥ 10 mmHg): measured by erect and supine blood pressures. Insufficient data to calculate sensitivity/specificity (data missing). Serum sodium (<135 mmol/l)

Reference	**Abbott 1995[1]**				
	Serum potassium (>5 mmol/l) Reference standard Serum cortisol was measured immediately before and 30 mins after an injection of 250µg Synacthen (tetracosactrin). Cortisol responses were graded according to the 'post' value achieved. A 'normal' response was defined as a post-stimulation cortisol of ≥450 nmol/l (16 µg/dl), an 'abnormal' response was defined as a post stimulation cortisol <350 nmol/L (12.5µg/dl), and an 'impaired' response was any intermediate result. Time between measurement of index test and reference standard: not reported				
2×2 tables		Reference standard +	Reference standard −	Total	Fatigue ≥2
	Index test +	12	26	38	
	Index test −	2	9	11	
	Total	14	35	49	
		Reference standard +	Reference standard −	Total	Fatigue ≥3
	Index test +	4	9	13	
	Index test −	10	26	36	
	Total	14	35	49	
		Reference standard +	Reference standard −	Total	Serum sodium (<135 mmol/l)
	Index test +	1	6	7	
	Index test −	13	29	42	
	Total	14	35	49	
		Reference standard +	Reference standard −	Total	Serum potassium (>5 mmol/l)
	Index test +	0	1	1	
	Index test −	14	34	48	
	Total	14	35	49	
Statistical measures	Index text: fatigue ≥2 Sensitivity: 0.86 (95% CI 0.57-0.98) Specificity: 0.26 (95% CI 0.12-0.43)				

Reference	Abbott 1995[1]
	PPV: 0.32 NPV: 0.82 PLR: 1.15 NLR: 0.56 Index text: fatigue ≥2 Sensitivity: 0.29 (95% CI 0.08-0.58) Specificity: 0.74 (95% CI 0.57-0.88) PPV: 0.31 NPV: 0.72 PLR: 1.11 NLR: 0.96 Index text: serum sodium (<135 mmol/l) Sensitivity: 0.07 (95% CI 0.00-0.34) Specificity: 0.83 (95% CI 0.66-0.93) PPV: 0.14 NPV: 0.69 PLR: 0.42 NLR: 1.12 Index text: serum potassium (>5 mmol/l) Sensitivity: 0.00 (95% CI 0.00-0.23) Specificity: 0.97 (95% CI 0.85-1.00) PPV: 0.00 NPV: 0.71 PLR: 0.00 NLR: 1.03
Source of funding	Not reported
Limitations	Risk of bias: very serious (unclear reporting on patient selection; whether index tests and reference standard were conducted without knowledge of the other's results; or timing between index test and reference standard) Indirectness: serious population indirectness (concerns over applicability of evidence from HIV population to general population)

Reference	**Abbott 1995[1]**
Comments	Study reports systolic postural drop (≥ 10 mmHg), measured by erect and supine blood pressures, but insufficient data to calculate sensitivity/specificity (data missing). Since no separate differences in clinical and biochemical features were demonstrated between patients with an impaired and those with an abnormal test result, the two were grouped together by the study authors for the purposes of statistical evaluation. Diagnostic accuracy data calculated by NICE from raw data

Reference	**Casanova-Cardiel 2003[2]**
Study type	Prospective cohort study (index test and reference standard data collected cross-sectionally)
Study methodology	Data source: patients with HIV-infection Recruitment: From January to August 2000, adult patients with HIV-infection and CD4 counts less than 200/mm^3were recruited from a single hospital
Number of patients	Total n = 106 (n with AI dependent on criteria used)
Patient characteristics	Age, mean (range): 37.7 (20-65) years. Gender (male to female ratio): 94:12 Ethnicity: not reported Setting: Department of Infectious Diseases of Adults, single hospital Country: Mexico Inclusion criteria: one or more clinical or laboratory determination suggesting adrenal insufficiency: tiredness, weakness, wasting syndrome, weight loss, anorexia, hyperpigmentation, dizziness, nausea, vomiting, diarrhoea, hypotension, hyponatremia, and/or hyperkalaemia. Exclusion criteria: under steroidal, ketoconazole or megestrol therapies.
Target condition(s)	Adrenal insufficiency

Reference	**Casanova-Cardiel 2003[2]**				
Index test(s) and reference standard	Index tests A questionnaire was designed to ask for several symptoms and signs: Fatigue Weight loss Salt intake Diarrhoea Skin hyperpigmentation Mucoses hyperpigmentation Orthostatic hypotension Hyponatraemia (serum Na < 135 mEq/L) Hyperkalaemia (serum Potassium > 5 mEq/L) Reference standard Low dose (10µg 1.V. bolus dose of synthetic ACTH-Cortrosyn, Organon Inc., West Orange. NJ, USA) short ACTH test was performed between 08.00 and 09.00 hours; basal ACTH, cortisol, and aldosterone and 60 min cortisol and aldosterone, were determined by RIA (all kits from CIS bio international). Abnormal response considered when cortisol peak response at 60 min was < 11 µg (Δ 11) with respect to basal; also analysed the data with three different criteria to define subnormal response to ACTH-stimulation test: 1) twofold value of basal cortisol; 2) any cortisol value above 18 µg/dL; and 3) any cortisol value above 20 µg/dL. Time between measurement of index test and reference standard: not reported.				
2×2 table (AI: cortisol peak response at 60 min < 11 µg (Δ 11) with respect to basal)		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	34	40	74	
	Index test −	13	19	32	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	32	39	71	
	Index test −	15	20	35	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	7	14	21	
	Index test −	40	45	85	

Reference	**Casanova-Cardiel 2003[2]**				
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	8	13	21	
	Index test −	39	46	85	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	19	22	41	
	Index test −	28	37	65	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	3	4	7	
	Index test −	44	55	99	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	16	20	36	
	Index test −	31	39	70	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	24	21	45	
	Index test −	23	38	61	
	Total	47	59	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	5	7	12	
	Index test −	42	52	94	
	Total	47	59	106	
2×2 table (AI: twofold value		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	58	16	74	
	Index test −	20	12	32	

Reference	**Casanova-Cardiel 2003[2]**				
of basal cortisol)	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	56	15	71	
	Index test −	22	13	35	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	15	6	21	
	Index test −	63	22	85	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	17	4	21	
	Index test −	61	24	85	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	31	10	41	
	Index test −	47	18	65	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	3	4	7	
	Index test −	75	24	99	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	24	12	36	
	Index test −	54	16	70	
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	36	9	45	
	Index test −	42	19	61	

Reference	**Casanova-Cardiel 2003[2]**				
	Total	78	28	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	10	2	12	
	Index test −	68	26	94	
	Total	78	28	106	
2×2 table (AI: any cortisol value > 18 µg/dL)		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	2	72	74	
	Index test −	3	29	32	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	4	67	71	
	Index test −	1	34	35	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	1	20	21	
	Index test −	4	81	85	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	0	21	21	
	Index test −	5	80	85	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	1	40	41	
	Index test −	4	61	65	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	1	6	7	
	Index test −	4	95	99	

Reference	Casanova-Cardiel 2003[2]				
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	2	34	36	
	Index test −	3	67	70	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	2	43	45	
	Index test −	3	58	61	
	Total	5	101	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	3	9	12	
	Index test −	2	92	94	
	Total	5	101	106	
2×2 table (AI: any cortisol value > 20 µg/dL)		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	2	72		
	Index test −	4	28		
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	5	66	71	
	Index test −	1	34	35	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Salt intake
	Index test +	1	20	21	
	Index test −	5	80	85	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	0	21	21	
	Index test −	6	79	85	

Reference	**Casanova-Cardiel 2003[2]**				
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	2	39	41	
	Index test −	4	61	65	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Mucoses hyperpigmentation
	Index test +	1	6	7	
	Index test −	5	94	99	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	2	34	36	
	Index test −	4	66	70	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Hyponatraemia (serum Na < 135 mEq/L)
	Index test +	2	43	45	
	Index test −	4	57	61	
	Total	6	100	106	
		Reference standard +	Reference standard −	Total	Hyperkalaemia (serum Potassium > 5 mEq/L)
	Index test +	3	9	12	
	Index test −	3	91	94	
	Total	6	100	106	
Statistical measures	**Criteria for reference standard positivity: cortisol peak response at 60 min < 11 µg (Δ 11) with respect to basal** Index text: lethargy (fatigue) Sensitivity: 0.72 (95% CI 0.57-0.84) Specificity: 0.32 (95% CI 0.21-0.46) PPV: 0.46 NPV: 0.59 PLR: 1.07				

Reference	Casanova-Cardiel 2003[2]
	NLR: 0.86 Index text: weight loss Sensitivity: 0.68 (95% CI 0.53-0.81) Specificity: 0.34 (95% CI 0.22-0.47) PPV: 0.45 NPV: 0.57 PLR: 1.03 NLR: 0.94 Index text: salt intake Sensitivity: 0.15 (95% CI 0.06-0.28) Specificity: 0.76 (95% CI 0.63-0.86) PPV: 0.33 NPV: 0.53 PLR: 0.63 NLR: 1.12 Index text: diarrhoea Sensitivity: 0.17 (95% CI 0.08-0.31) Specificity: 0.78 (95% CI 0.65-0.88) PPV: 0.38 NPV: 0.54 PLR: 0.77 NLR: 1.06 Index text: skin hyperpigmentation Sensitivity: 0.40 (95% CI 0.26-0.56) Specificity: 0.63 (95% CI 0.49-0.75) PPV: 0.46 NPV: 0.57 PLR: 1.08 NLR: 0.95 Index text: mucoses hyperpigmentation Sensitivity: 0.06 (95% CI 0.01-0.18)

Reference	Casanova-Cardiel 2003[2]
	Specificity: 0.93 (95% CI 0.84-0.98) PPV: 0.43 NPV: 0.56 PLR: 0.94 NLR: 1.00 Index text: orthostatic hypotension Sensitivity: 0.34 (95% CI 0.21-0.49) Specificity: 0.66 (95% CI 0.53-0.78) PPV: 0.44 NPV: 0.56 PLR: 1.00 NLR: 1.00 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.51 (95% CI 0.36-0.66) Specificity: 0.64 (95% CI 0.51-0.76) PPV: 0.53 NPV: 0.62 PLR: 1.43 NLR: 0.76 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.11 (95% CI 0.04-0.23) Specificity: 0.88 (95% CI (0.77-0.95) PPV: 0.42 NPV: 0.55 PLR: 0.90 NLR: 1.01 **Criteria for reference standard positivity: twofold value of basal cortisol** Index text: lethargy (fatigue) Sensitivity: 0.74 (95% CI 0.63-0.84) Specificity: 0.43 (95% CI 0.24-0.63) PPV: 0.78

Reference	Casanova-Cardiel 2003[2]
	NPV: 0.38 PLR: 1.30 NLR: 0.60 Index text: weight loss Sensitivity: 0.72 (95% CI 0.60-0.81) Specificity: 0.46 (95% CI 0.28-0.66) PPV: 0.79 NPV: 0.37 PLR: 1.34 NLR: 0.61 Index text: salt intake Sensitivity: 0.19 (95% CI 0.11-0.30) Specificity: 0.79 (95% CI 0.59-0.92) PPV: 0.71 NPV: 0.26 PLR: 0.90 NLR: 1.03 Index text: diarrhoea Sensitivity: 0.22 (95% CI 0.13-0.33) Specificity: 0.86 (95% CI 0.67-0.96) PPV: 0.81 NPV: 0.28 PLR: 1.53 NLR: 0.91 Index text: skin hyperpigmentation Sensitivity: 0.40 (95% CI 0.29-0.51) Specificity: 0.64 (95% CI 0.44-0.81) PPV: 0.76 NPV: 0.28 PLR: 1.11 NLR: 0.94

Reference	Casanova-Cardiel 2003[2]
	Index text: mucoses hyperpigmentation Sensitivity: 0.04 (95% CI 0.01-0.11) Specificity: 0.86 (95% CI 0.67-0.96) PPV: 0.43 NPV: 0.24 PLR: 0.27 NLR: 1.12 Index text: orthostatic hypotension Sensitivity: 0.31 (95% CI 0.21-0.42) Specificity: 0.57 (95% CI 0.37-0.76) PPV: 0.67 NPV: 0.23 PLR: 0.72 NLR: 1.21 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.46 (95% CI 0.35-0.58) Specificity: 0.68 (95% CI 0.48-0.84) PPV: 0.80 NPV: 0.31 PLR: 1.44 NLR: 0.79 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.13 (95% CI 0.06-0.22) Specificity: 0.93 (95% CI 0.76-0.99) PPV: 0.83 NPV: 0.28 PLR: 1.79 NLR: 0.94 **Criteria for reference standard positivity: any cortisol value > 18 µg/dL** Index text: lethargy (fatigue) Sensitivity: 0.40 (95% CI 0.05-0.85)

Reference	Casanova-Cardiel 2003[2]
	Specificity: 0.29 (95% CI 0.20-0.39) PPV: 0.03 NPV: 0.91 PLR: 0.56 NLR: 2.09 Index text: weight loss Sensitivity: 0.80 (95% CI 0.28-0.99) Specificity: 0.34 (95% CI 0.25-0.44) PPV: 0.06 NPV: 0.97 PLR: 1.21 NLR: 0.59 Index text: salt intake Sensitivity: 0.20 (95% CI 0.01-0.72) Specificity: 0.80 (95% CI 0.71-0.87) PPV: 0.05 NPV: 0.95 PLR: 1.01 NLR: 1.00 Index text: diarrhoea Sensitivity: 0.00 (95% CI 0.00-0.52) Specificity: 0.79 (95% CI 0.70-0.87 PPV: 0.00 NPV: 0.94 PLR: 0.00 NLR: 1.26 Index text: skin hyperpigmentation Sensitivity: 0.20 (95% CI 0.01-0.72) Specificity: 0.60 (95% CI 0.50-0.70) PPV: 0.02 NPV: 0.94 PLR: 0.51

Reference	Casanova-Cardiel 2003[2]
	NLR: 1.32 Index text: mucoses hyperpigmentation Sensitivity: 0.20 (95% CI 0.01-0.72) Specificity: 0.94 (95% CI 0.88-0.98) PPV: 0.14 NPV: 0.96 PLR: 3.37 NLR: 0.85 Index text: orthostatic hypotension Sensitivity: 0.40 (95% CI (0.05-0.85) Specificity: 0.66 (95% CI 0.56-0.75) PPV: 0.06 NPV: 0.96 PLR: 1.19 NLR: 0.90 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.40 (95% CI 0.05-0.85) Specificity: 0.57 (95% CI 0.47-0.67) PPV: 0.04 NPV: 0.95 PLR: 0.94 NLR: 1.04 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.60 (95% CI 0.15-0.95) Specificity: 0.91 (95% CI 0.84-0.96) PPV: 0.25 NPV: 0.98 PLR: 6.73 NLR: 0.44 **Criteria for reference standard positivity: any cortisol value > 20 µg/dL**

Reference	Casanova-Cardiel 2003[2]
	Index text: lethargy (fatigue) Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.28 (95% CI 0.19-0.38) PPV: 0.03 NPV: 0.88 PLR: 0.46 NLR: 2.38 Index text: weight loss Sensitivity: 0.83 (95% CI 0.36-1.00) Specificity: 0.34 (95% CI 0.25-0.44) PPV: 0.07 NPV: 0.97 PLR: 1.26 NLR: 0.49 Index text: salt intake Sensitivity: 0.17 (95% CI 0.00-0.64) Specificity: 0.80 (95% CI 0.71-0.87) PPV: 0.05 NPV: 0.94 PLR: 0.83 NLR: 1.04 Index text: diarrhoea Sensitivity: 0.00 (95% CI 0.00-0.46) Specificity: 0.79 (95% CI 0.70-0.87) PPV: 0.00 NPV: 0.93 PLR: 0.00 NLR: 1.27 Index text: skin hyperpigmentation Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.61 (95% CI 0.51-0.71) PPV: 0.05

Reference	Casanova-Cardiel 2003[2]
	NPV: 0.94 PLR: 0.85 NLR: 1.09 Index text: mucoses hyperpigmentation Sensitivity: 0.17 (95% CI 0.00-0.64) Specificity: 0.94 (95% CI 0.87-0.98) PPV: 0.14 NPV: 0.95 PLR: 2.78 NLR: 0.89 Index text: orthostatic hypotension Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.66 (95% CI 0.56-0.75) PPV: 0.06 NPV: 0.94 PLR: 0.98 NLR: 1.01 Index text: hyponatraemia (serum Na < 135 mEq/L) Sensitivity: 0.33 (95% CI 0.04-0.78) Specificity: 0.57 (95% CI 0.47-0.67) PPV: 0.04 NPV: 0.93 PLR: 0.78 NLR: 1.17 Index text: hyperkalaemia (serum Potassium > 5 mEq/L) Sensitivity: 0.50 (95% CI 0.12-0.88) Specificity: 0.91 (95% CI 0.84-0.96) PPV: 0.25 NPV: 0.97 PLR: 5.56 NLR: 0.55

Reference	**Casanova-Cardiel 2003[2]**
Source of funding	Not reported
Limitations	Risk of bias: very serious (unclear reporting on patient selection; unclear application of the index test; unclear application of the reference standard (unclear if blinded); or timing between index test and reference standard) Indirectness: very serious (serious population indirectness due to concerns over applicability of evidence from a population diagnosed with AIDS to the general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 10 µg ACTH test)
Comments	95% CIs calculated by NICE from raw data

Reference	**Hintong 2021 ID[3]**
Study type	Cross-sectional diagnostic accuracy
Study methodology	Data source: Cross-sectional study conducted with 42 patients who were seen at the dermatology outpatient departments at the Faculty of Medicine, Chiang Mai University Hospital over a 5-month period (June – October 2020). Recruitment: Recruited participants were adult dermatological patients (≥18 years) who had used topical corticosteroids for at least 12 months.
Number of patients	Total n= 42. Adrenal insufficiency n =17. Without adrenal insufficiency n= 25
Patient characteristics	Age, mean (SD): 56.5 ±15.4 years Gender (male to female ratio): 30:12 Ethnicity: NR Setting: Dermatology outpatient department Country: Thailand Inclusion criteria: Adult patients with dermatological conditions who had been prescribed topical steroids for at least 12 months by the dermatology outpatient departments of the Faculty of Medicine, Chiang Mai University from June through October 2020 were included.

Reference	**Hintong 2021 ID[3]**				
	Exclusion criteria: Patients with pituitary or adrenal diseases, pregnant women and patients who had been treated with either systemic corticosteroids or other local corticosteroids were excluded. Treatment: The mean duration of treatment was 10.1 ± 6 years Skin condition: The majority of patients had psoriasis (n = 14, 82.4%)				
Target condition(s)	Adrenal insufficiency				
Index test(s) and reference standard	Index test Symptoms of AI included lethargy, nausea and vomiting, orthostatic hypotension and significant weight loss. Significant weight loss was defined as a loss of 5% of body weight in one month or a loss of 10% over a period of six months. Reference standard An 8AM cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL at 20 or 40 minutes after a 5 µg ACTH stimulation test was defined as having AI. Patients were instructed to suspend use of topical corticosteroids for at least 24 hours before serum morning cortisol measurement and ACTH stimulation tests. In those with serum morning cortisol between 3 and 17.9 µg/dL, ACTH stimulation tests were performed on the same day between 9–11AM to either exclude or diagnose AI. Serum cortisol levels were measured by electrochemiluminescence assay (ECLIA) (Elecsys ® Cortisol II assay, Roche Diagnostics GmbH, Mannheim, Germany). Time between measurement of index test and reference standard: Not reported				
2×2 table		Reference standard +	Reference standard −	Total	Lethargy
	Index test +	0	1	1	
	Index test −	17	24	41	
	Total	17	25	42	
		Reference standard +	Reference standard −	Total	Nausea and vomiting
	Index test +	0	0	0	
	Index test −	17	25	42	
	Total	17	25	42	
		Reference standard +	Reference standard −	Total	Orthostatic hypotension
	Index test +	0	0	0	
	Index test −	17	25	42	
	Total	17	25	42	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	1	0	1	

Reference	**Hintong 2021 ID[3]**				
	Index test −	16	25	41	
	Total	17	25	42	
Statistical measures	Index text: lethargy Sensitivity: 0.00 (95% CI 0.00-0.20) Specificity: 0.96 (95% CI 0.80-1.00) PPV: 0.00 NPV: 0.59 PLR: 0.00 NLR: 1.04 Index text: nausea and vomiting Sensitivity: 0.00 (95% CI 0.00-0.20) Specificity: 1.00 (95% CI 0.86-1.00) PPV: - NPV: 0.60 PLR: - NLR: 1.00 Index test: orthostatic hypotension Sensitivity: 0.00 (95% CI 0.00-0.20) Specificity: 1.00 (95% CI 0.86-1.00) PPV: - NPV: 0.60 PLR: - NLR: 1.00 Index test: weight loss Sensitivity: 0.06 (95% CI 0.00-0.29) Specificity: 1.00 (95% CI 0.86-1.00) PPV: 1.00 NPV: 0.61 PLR: - NLR: 0.94				
Source of funding	Not reported				

Reference	Hintong 2021 ID[3]
Limitations	Risk of bias: very serious (unclear reporting on patient selection; whether index tests and reference standard were conducted without knowledge of the other's results; or timing between index test and reference standard) Indirectness: very serious (serious population indirectness (concerns over applicability of evidence from long term topical steroid use population to the general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 5 µg ACTH test)
Comments	Diagnostic accuracy data calculated by NICE from raw data

Reference	Mabuza 2020 ID[4]
Study type	Cross-sectional
Study methodology	Data source: A researcher administered questionnaire was used to collect data related to signs, symptoms, and laboratory findings of TB-suspect patients admitted to the three hospitals over a six months' period. Data comprised baseline characteristics (age, sex, marital status, and educational level); symptoms of AI (dry itchy skin, muscle and joint pains, tiredness, craving for salt, loss of libido in males, amenorrhoea in females, dizziness, loss of weight and nausea and vomiting) and signs of AI (systolic hypotension, low pulse volume, tachycardia, hypothermia, mucosal and skin hyperpigmentation, and general body wasting). Serum cortisol, sodium, potassium, and fasting serum glucose to establish patients' electrolyte status vis-à-vis cortisol levels were also conducted. Recruitment: study population consisted of all TB-suspect patients admitted to the three hospitals over a six months' period (1st September 2014 - 28th February 2015), which worked out to the following numbers: DGMAH (ward 35), 31 patients, ODH, 23 and JDH 38, giving a total of 92 patients.
Number of patients	Total n = 92 (n=75 analysed). Adrenal insufficiency n = 28, no adrenal insufficiency n = 47.
Patient characteristics	Age, mean (SD): 40.3 (15.7) Gender (male to female ratio): 43:32 Ethnicity: NR Setting: Tertiary hospital located in Pretoria, and two referring district hospitals

Reference	**Mabuza 2020 ID[4]**				
	Country: South Africa Inclusion criteria: The study population consisted of all TB-suspect patients admitted to the three hospitals over a six months' period (1st September 2014 - 28th February 2015). Exclusion criteria: NR				
Target condition(s)	Adrenal insufficiency				
Index test(s) and reference standard	Index tests Three medical officers (one for each setting) were hired to collect data. They used the researcher-administered data collection sheets. Data comprised baseline characteristics and symptoms of AI (dry itchy skin, muscle and joint pains, tiredness, craving for salt, loss of libido in males, amenorrhoea in females, dizziness, loss of weight and nausea and vomiting) and signs of AI (systolic hypotension, low pulse volume, tachycardia, hypothermia, mucosal and skin hyperpigmentation and general body wasting). systolic hypotension skin hyperpigmentation salt craving weight loss nausea vomiting tiredness Reference standard The low-dose (1µg/ml intravenously) short corticotropin (Synacthen®) stimulation test was used. The test drug was administered to patients between 07h00 and 09h00. The low dose Synacthen solution was constituted as follows: one ampoule of 250µg of Synacthen diluted into 249ml of sterile 0.9% saline solution to obtain a concentration of 1µg/ml. This procedure was carried out by the three data collectors in the wards under sterile conditions, each using a graduated measuring jar to prepare the solution. Two blood samples from each patient were taken to measure the pre-corticotropin and post-corticotropin serum cortisol levels. The time interval between the first and second specimens was 30 - 60 minutes. All the assays were performed in one reference laboratory, the National Health Laboratory Service (NHLS), at Dr George Mukhari Academic Hospital. (AI definition = serum cortisol level < 500nmol/L) Time between measurement of index test and reference standard: No details provided for all tests.				
2×2 table		Reference standard +	Reference standard −	Total	Systolic hypotension
	Index test +	24	42	66	

Reference	Mabuza 2020 ID[4]				
	Index test −	4	5	9	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Skin hyperpigmentation
	Index test +	22	35	57	
	Index test −	6	12	18	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Salt craving
	Index test +	23	38	61	
	Index test −	5	9	14	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	6	3	9	
	Index test −	22	44	66	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Nausea
	Index test +	16	21	37	
	Index test −	12	26	38	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Vomiting
	Index test +	19	35	54	
	Index test −	9	12	21	
	Total	28	47	75	
		Reference standard +	Reference standard −	Total	Tiredness
	Index test +	7	7	14	
	Index test −	21	40	61	
	Total	28	47	75	

Reference	Mabuza 2020 ID[4]
Statistical measures	Index text: Hypotension Sensitivity: 0.86 (95% CI 0.67-0.96) Specificity: 0.11 (95% CI 0.04-0.23) PPV: 0.36 NPV: 0.56 PLR: 0.96 NLR: 1.34 Index text: Skin hyperpigmentation Sensitivity: 0.79 (95% CI 0.59-0.92) Specificity: 0.26 (95% CI 0.14-0.40) PPV: 0.39 NPV: 0.67 PLR: 1.06 NLR: 0.84 Index text: Salt craving Sensitivity: 0.82 (95% CI 0.63-0.94) Specificity: 0.19 (95% CI 0.09-0.33) PPV: 0.38 NPV: 0.64 PLR: 1.02 NLR: 0.93 Index text: Weight loss Sensitivity: 0.21 (95% CI 0.08-0.41) Specificity: 0.94 (95% CI 0.82-0.99) PPV: 0.67 NPV: 0.67 PLR: 3.36 NLR: 0.84 Index text: Nausea Sensitivity: 0.57 (95% CI 0.37-0.76) Specificity: 0.55 (95% CI 0.40-0.70) PPV: 0.43

Reference	Mabuza 2020 ID[4]
	NPV: 0.68 PLR: 1.28 NLR: 0.77 Index text: Vomiting Sensitivity: 0.68 (95% CI 0.48-0.84) Specificity: 0.26 (95% CI 0.14-0.40) PPV: 0.35 NPV: 0.57 PLR: 0.91 NLR: 1.26 Index text: Tiredness Sensitivity: 0.25 (95% CI 0.11-0.45) Specificity: 0.85 (95% CI 0.72-0.94) PPV: 0.50 NPV: 0.66 PLR: 1.68 NLR: 0.88
Source of funding	This study was funded through the VLIR (Belgium) Grant Number: ZA2020IUC021A102.
Limitations	Risk of bias: very serious (unclear patient selection (no information provided), unclear application of the index test, unclear application of the reference standard (unclear if blinded) and high risk of bias arising from the patient flow (17 of 92 missing data sheets) Indirectness: Not serious
Comments	Diagnostic accuracy data calculated by NICE from raw data

Reference	Naguib 2022[5]
Study type	Cross-sectional study
Study methodology	Data source: clinical and laboratory tests of 132 individuals with liver cirrhosis Recruitment: The study included 132 individuals with liver cirrhosis who were recruited from Alexandria Main University Hospital, Internal Medicine Department, Hepatology Outpatient Clinic between February and June 2021.

Reference	Naguib 2022[5]
Number of patients	Total n = 132. Adrenal insufficiency n = 85. Normal adrenal function n = 46
Patient characteristics	Age, mean (SD): 55.2 (8.9) years Gender (male to female ratio): 84:48 Ethnicity: NR Setting: Tertiary care hospital Country: Egypt Inclusion criteria: Patients were considered for the study if they met the following criteria: age 18 years and above, hemodynamically stable with a mean arterial pressure (MAP) > 70 mm Hg and not on vasopressors. Exclusion criteria: The following were the criteria for exclusion: history of pituitary or adrenal disease, taking steroids or other medicines that affect cortisol production (eg, etomidate, ketoconazole), severe cardiopulmonary and kidney disease, hepatocellular carcinoma, critical illness, sepsis, active infection, receiving oral or parenteral antibiotic therapy within the last 30 days before enrolment and pregnancy.
Target condition(s)	Adrenal insufficiency
Index test(s) and reference standard	Index test Hyponatraemia < 135mEq/l. The clinical information of the patients, including basic demographics, clinical features, additional comorbidities, and the results of routine laboratory tests, was recorded. No further details provided. Reference standard The adrenal function of all subjects was evaluated by measuring basal and peak cortisol after 60 minutes following the short Synacthen test (SST). Basal cortisol was defined as the morning cortisol concentration (between 8:00 and 9:00 am) before Synacthen administration. The highest cortisol concentration at 60 minutes after 250 µg Synacthen injection was considered as peak cortisol. A normal response to the Synacthen stimulation test (SST) was defined as a peak total serum cortisol concentration of at least 18 µg/dl. For the purposes of this study, AI was defined as having a basal cortisol of less than 9 µg/dl and/or a peak cortisol of less than 18 µg/dl. Time between measurement of index test and reference standard: Not reported.

Reference	**Naguib 2022[5]**				
2×2 table		Reference standard +	Reference standard −	Total	Hyponatraemia (< 135mEq/l)
	Index test +	32	4	36	
	Index test −	54	42	96	
	Total	86	46	132	
Statistical measures	Index text: Hyponatraemia (< 135mEq/l) Sensitivity: 0.37 (95% CI 0.27- 0.48) Specificity: 0.91 (95% CI 0.79 - 0.98) PPV: 0.89 NPV: 0.44 PLR: 4.28 NLR: 0.69				
Source of funding	This research was funded by the Deanship of Scientific Research at Princess Nourah bint Abdulrahman University through the Fast-track Research Funding Program				
Limitations	Risk of bias: serious (unclear patient selection (no information provided), unclear application of the reference standard (unclear if blinded) and unclear timing between index test and reference standard) Indirectness: serious population indirectness (concerns over applicability of evidence from people with stable liver cirrhosis to general population)				
Comments	Diagnostic accuracy data calculated by NICE from raw data				

Reference	**Wolff 2001[7]**
Study type	Prospective cohort study (index test and reference standard data collected cross-sectionally)
Study methodology	Data source: Patients with a confirmed diagnosis of AIDS. Recruitment: Between July 1996 and March 1998, 272 patients with a presumptive diagnosis of AIDS admitted to the Hospital de Clínicas de Porto Alegre for treatment, were evaluated for entry to the study. Those meeting inclusion/exclusion criteria were enrolled.
Number of patients	Total n = 72, total analysed n = 63 (abnormal response to ACTH n = 12, normal rapid ACTH test n = 51)
Patient characteristics	Age, mean (range): 34.6 (16-62) years. Gender (male to female ratio): 50:13

Reference	**Wolff 2001[7]**				
	Ethnicity: 73% Caucasian Setting: single hospital Country: Brazil Inclusion criteria: confirmed diagnosis of AIDS, admitted to hospital for treatment. Exclusion criteria: diagnosis of AIDS not confirmed, using glucocorticoids or had used them during the month prior to the study, unable to sign the informed consent form or to answer the questionnaire, no venous line access, died or discharged before the ACTH test.				
Target condition(s)	Adrenal hypofunction				
Index test(s) and reference standard	Index tests A standard questionnaire and clinical examination were used to assess signs or symptoms that could be related to adrenal insufficiency (presence of weakness, fatigue, weight loss, anorexia, nausea, vomiting, diarrhoea, muscle or joint pain, arterial hypotension, hyperpigmentation, electrolyte abnormalities or a history of glucocorticoid use). Reference standard Low-dose ACTH test: 250 µg vial of 1-24 ACTH (Cortrosyn®, Organon International Oss) diluted in sterile saline solution to a concentration of 1 µg/mL. An indwelling intravenous catheter was inserted into the forearm between 7:00 a.m. and 8:00 a.m. Blood samples was taken right before, and 30 and 40 minutes following the injection of 1 mg of 1-24 ACTH. HPA axis considered as normal when the patient had a serum cortisol level ≥ 18 µg/dL in at least 1 measurement (based on measurements in healthy controls). Time between measurement of index test and reference standard: not reported.				
2×2 table		Reference standard +	Reference standard −	Total	Lethargy (fatigue)
	Index test +	9	27	36	
	Index test −	3	24	27	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Lethargy (weakness)
	Index test +	5	26	31	
	Index test −	7	25	32	
	Total	12	51	63	

Reference	**Wolff 2001[7]**				
		Reference standard +	Reference standard −	Total	Nausea
	Index test +	6	20	26	
	Index test −	6	31	37	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Vomiting
	Index test +	5	16	21	
	Index test −	7	35	42	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Diarrhoea
	Index test +	3	16	19	
	Index test −	9	35	44	
	Total	12	51	63	
		Reference standard +	Reference standard −	Total	Weight loss
	Index test +	10	36	46	
	Index test −	2	15	17	
	Total	12	51	63	
Statistical measures	<u>Index text: lethargy (fatigue)</u> Sensitivity: 0.75 (95% CI 0.43-0.95) Specificity: 0.47 (95% CI 0.33-0.62) PPV: 0.25 NPV: 0.89 PLR: 1.42 NLR: 0.53 <u>Index text: lethargy (weakness)</u> Sensitivity: 0.42 (95% CI 0.15-0.72) Specificity: 0.49 (95% CI 0.35-0.63) PPV: 0.16 NPV: 0.78 PLR: 0.82 NLR: 1.19				

Reference	Wolff 2001[7]
	Index text: nausea Sensitivity: 0.50 (95% CI 0.21-0.79) Specificity: 0.61 (95% CI 0.46-0.74) PPV: 0.23 NPV: 0.84 PLR: 1.28 NLR: 0.82 Index text: vomiting Sensitivity: 0.42 (95% CI 0.15-0.72) Specificity: 0.69 (95% CI 0.54-0.81) PPV: 0.24 NPV: 0.83 PLR: 1.33 NLR: 0.85 Index text: diarrhoea Sensitivity: 0.25 (95% CI 0.05-0.57) Specificity: 0.69 (95% CI 0.54-0.81) PPV: 0.16 NPV: 0.80 PLR: 0.80 NLR: 1.09 Index text: weight loss Sensitivity: 0.83 (95% CI 0.52-0.98) Specificity: 0.29 (95% CI 0.17-0.44) PPV: 0.22 NPV: 0.88 PLR: 1.18 NLR: 0.57
Source of funding	Rio Grande Research Support Foundation do Sul (FAPERGS).
Limitations	Risk of bias: very serious (unclear reporting on patient selection; whether reference standard was conducted without knowledge of index test results; or timing between index test and reference standard)

Reference	**Wolff 2001[7]**
	Indirectness: very serious (serious population indirectness due to concerns over applicability of evidence from AIDS population to general population; serious indirectness of the reference standard due to concerns over applicability of evidence on low dose 1 µg/mL ACTH test)
Comments	Diagnostic accuracy data calculated by NICE from raw data

Appendix E Forest plots

E.1 Coupled sensitivity and specificity forest plots.

E.1.1 Hypotension for diagnosing adrenal insufficiency.

Figure 2: Sensitivity and specificity of orthostatic hypotension for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

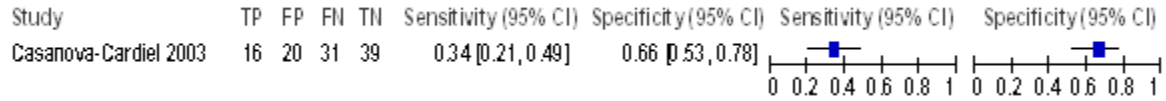


Figure 3: **Sensitivity and specificity of orthostatic hypotension for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection**

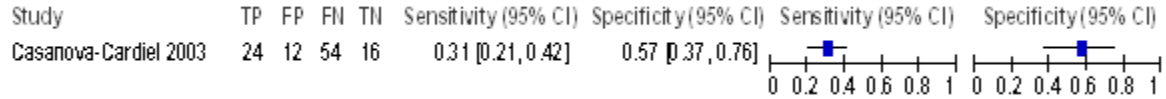


Figure 4: Sensitivity and specificity of orthostatic hypotension for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

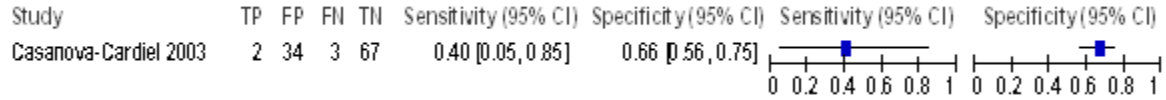


Figure 5: Sensitivity and specificity of orthostatic hypotension for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

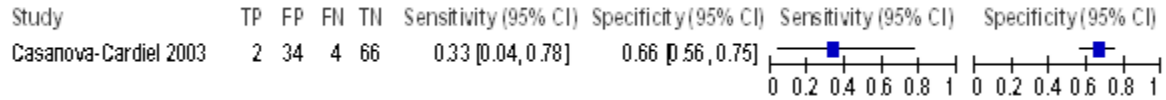
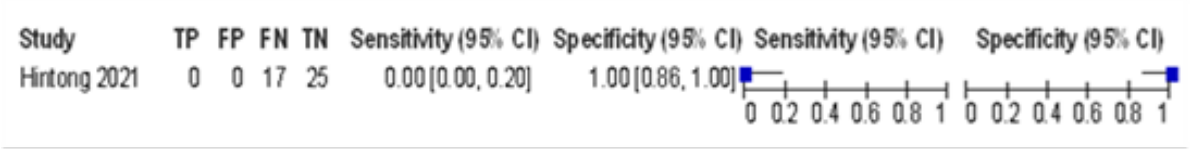


Figure 6: Sensitivity and specificity of orthostatic hypotension for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in people using topical steroids



E.1.2 Hyperpigmentation for diagnosing adrenal insufficiency.

Figure 7: **Sensitivity and specificity of skin hyperpigmentation for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection.**

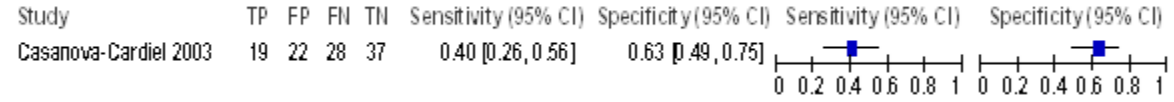


Figure 8: Sensitivity and specificity of skin hyperpigmentation for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

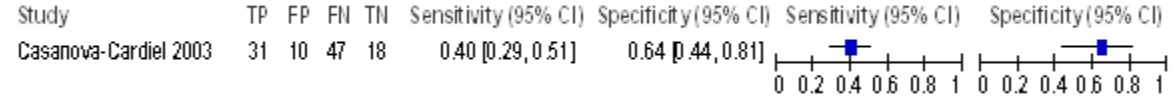


Figure 9: Sensitivity and specificity of skin hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

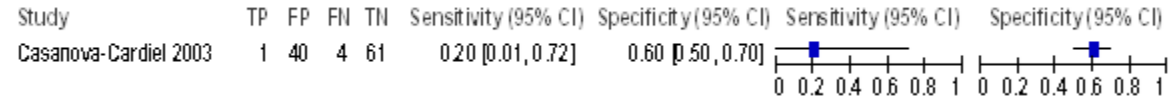


Figure 10: Sensitivity and specificity of skin hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

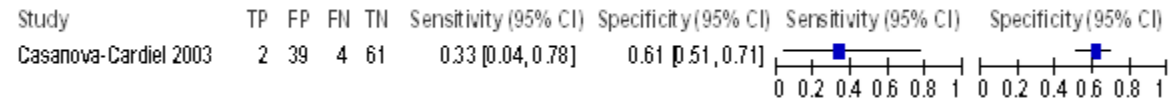
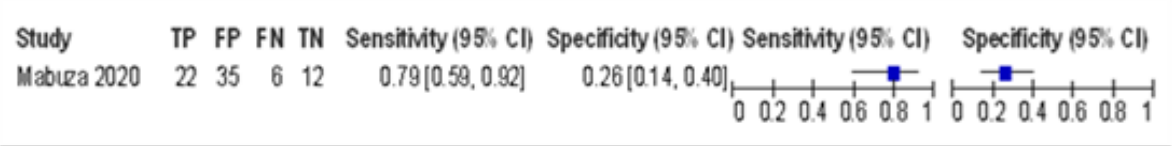


Figure 11: Sensitivity and specificity of skin hyperpigmentation for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB



E.1.3 Mucoses hyperpigmentation for diagnosing adrenal insufficiency

Figure 12: Sensitivity and specificity of mucoses hyperpigmentation for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

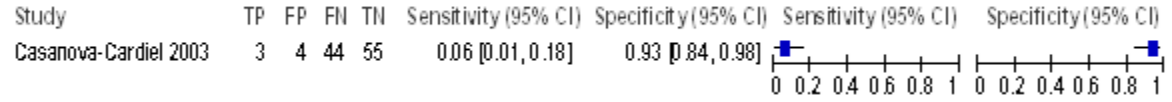


Figure 13: Sensitivity and specificity of mucoses hyperpigmentation for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

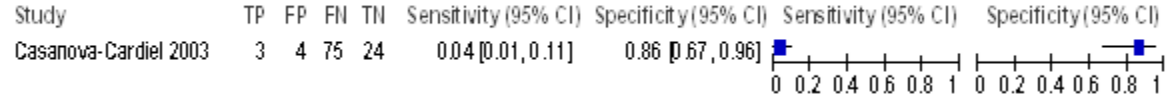


Figure 14: Sensitivity and specificity of mucoses hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

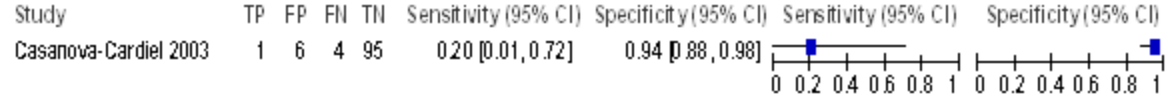
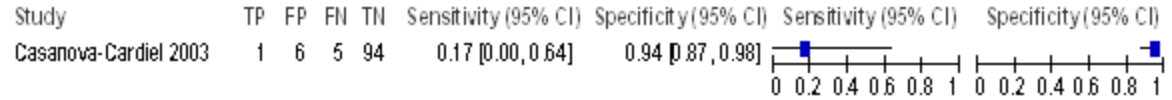


Figure 15: Sensitivity and specificity of mucoses hyperpigmentation for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection



E.1.4 Lethargy for diagnosing adrenal insufficiency.

Figure 16: Sensitivity and specificity of lethargy (fatigue ≥2) for diagnosing cortisol deficiency (cortisol <350 nmol/L or indeterminate result after 250µg Synacthen) in people with HIV-infection

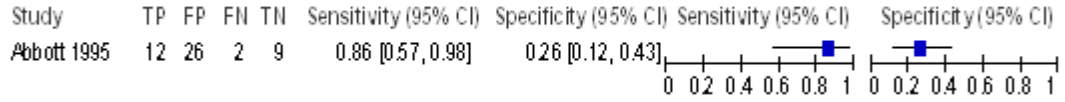


Figure 17: **Sensitivity and specificity of lethargy (fatigue ≥3) for diagnosing cortisol deficiency (cortisol <350 nmol/L or indeterminate result after 250µg Synacthen for diagnosing cortisol deficiency (cortisol <350 nmol/L or indeterminate result after 250µg Synacthen) in people with HIV-infection**

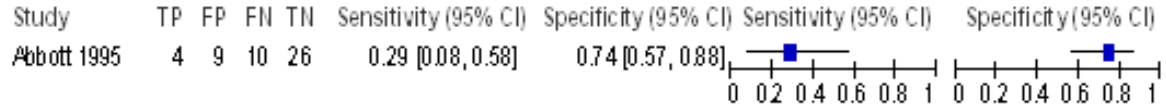


Figure 18: Sensitivity and specificity of lethargy (fatigue) for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

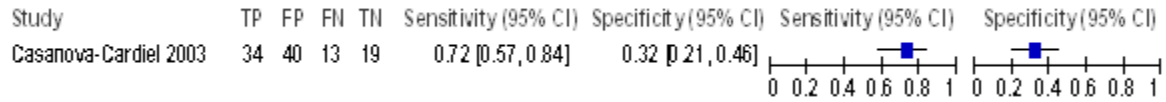


Figure 19: **Sensitivity and specificity of lethargy (fatigue) for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection**

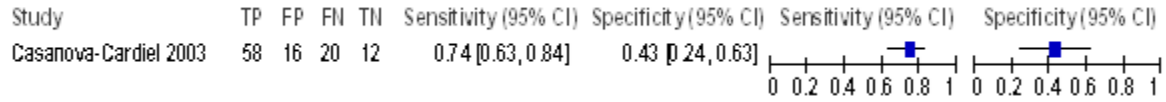


Figure 20: Sensitivity and specificity of lethargy (fatigue) for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

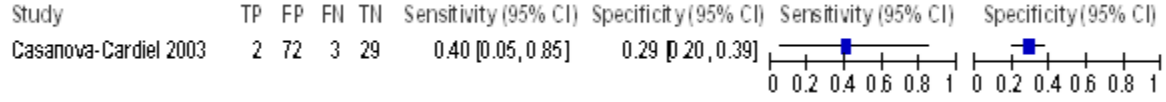


Figure 21: Sensitivity and specificity of lethargy (fatigue) for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

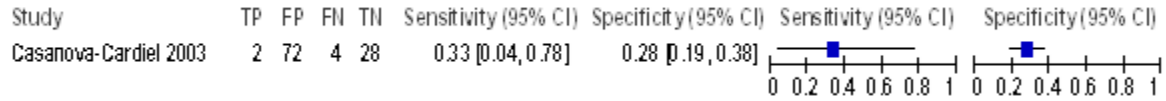


Figure 22: Sensitivity and specificity of lethargy for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in people using topical steroids

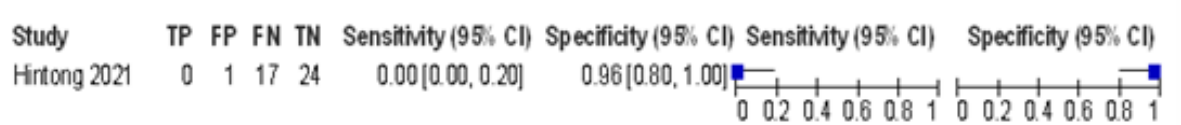


Figure 23: Sensitivity and specificity of lethargy (tiredness) for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB

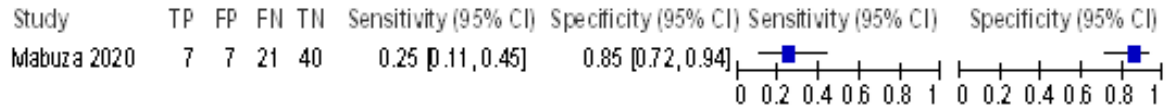


Figure 24: Sensitivity and specificity of lethargy (fatigue) for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS

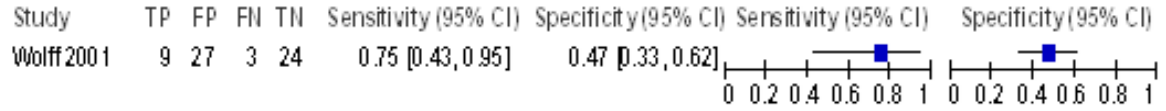
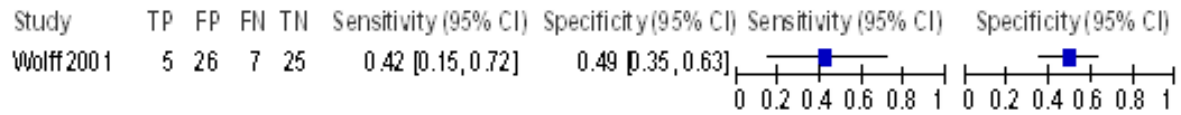


Figure 25: Sensitivity and specificity of lethargy (weakness) for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS



E.1.5 Salt craving for diagnosing adrenal insufficiency.

Figure 26: Sensitivity and specificity of salt intake for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

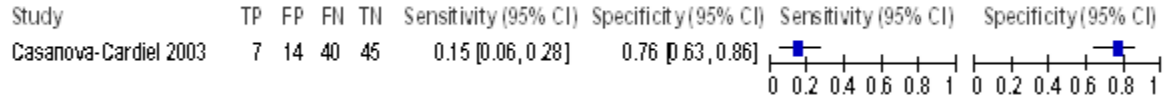


Figure 27: Sensitivity and specificity of salt intake for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

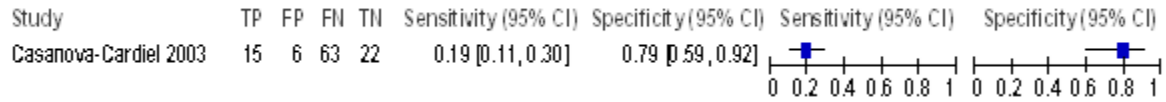


Figure 28: Sensitivity and specificity of salt intake for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

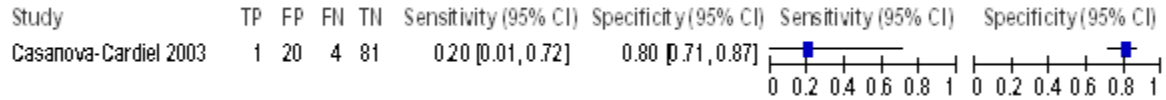


Figure 29: Sensitivity and specificity of salt intake for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

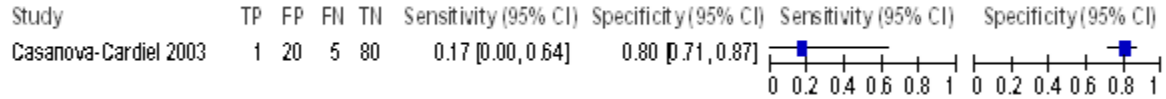
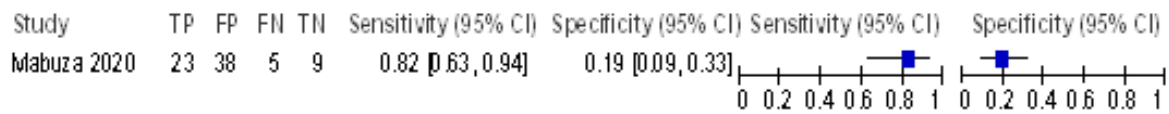


Figure 30: Sensitivity and specificity of salt craving for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen ®) stimulation test in people with suspected TB



E.1.6 Weight loss for diagnosing adrenal insufficiency.

Figure 31: Sensitivity and specificity of weight loss for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

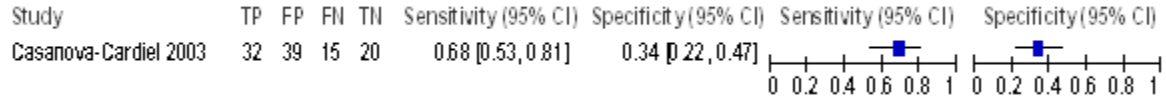


Figure 32: Sensitivity and specificity of weight loss for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

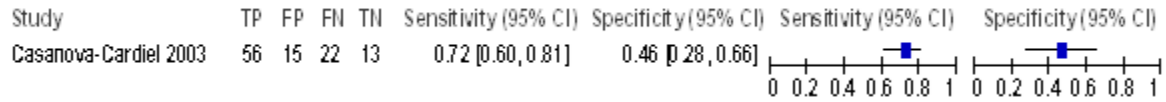


Figure 33: Sensitivity and specificity of weight loss for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

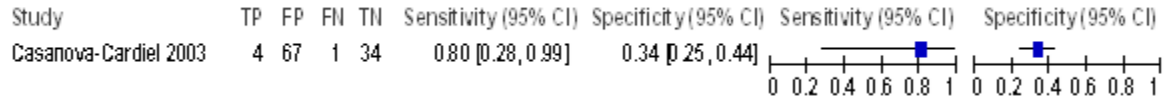


Figure 34: Sensitivity and specificity of weight loss for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

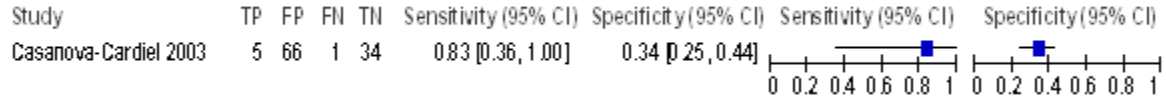


Figure 35: Sensitivity and specificity of weight loss for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in people using topical steroids

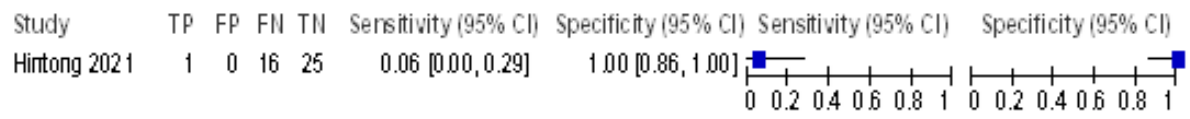


Figure 36: Sensitivity and specificity of weight loss for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB

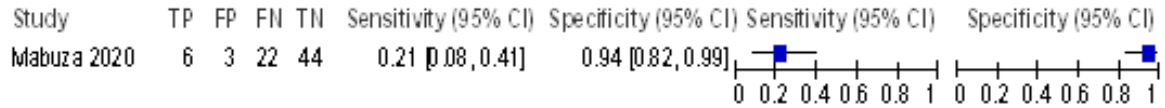


Figure 37: Sensitivity and specificity of weight loss for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS

E.1.7 Hyponatraemia (serum sodium (<135mEq/l) for diagnosing adrenal insufficiency

Figure 38: Sensitivity and specificity of hyponatraemia (serum Na < 135 mEq/L) for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

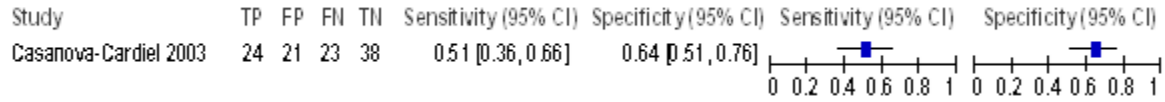


Figure 39: Sensitivity and specificity of hyponatraemia (serum Na < 135 mEq/L) for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

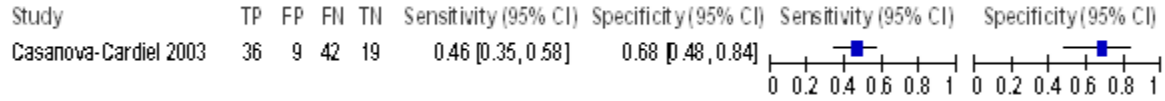


Figure 40: Sensitivity and specificity of hyponatraemia (serum Na < 135 mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

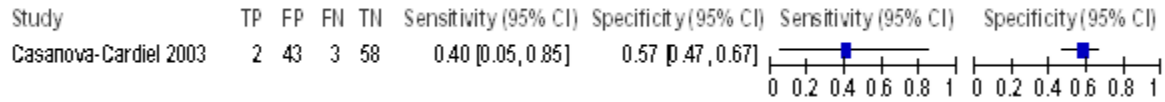


Figure 41: Sensitivity and specificity of hyponatraemia (serum Na < 135 mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

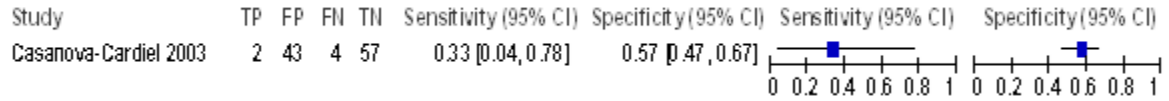
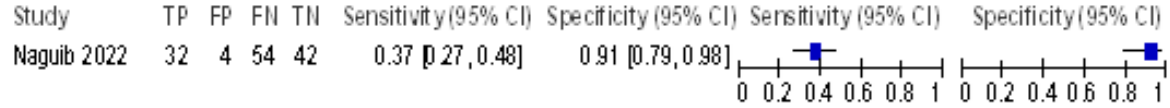


Figure 42: Sensitivity and specificity of hyponatraemia (<135mEq/l) for diagnosing adrenal insufficiency (basal cortisol < 9 µg/dl and/or peak cortisol < 18 µg/dl after short 250 µg Synacthen test) in people with stable liver cirrhosis



E.1.8 Hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency

Figure 43: Sensitivity and specificity of hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

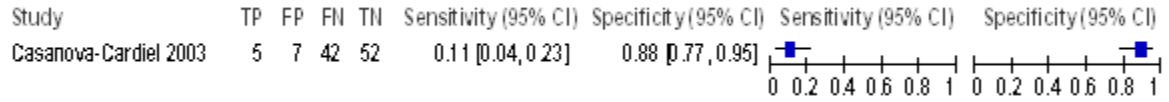


Figure 44: Sensitivity and specificity of hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

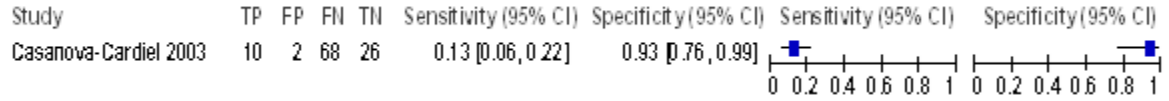


Figure 45: Sensitivity and specificity of hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

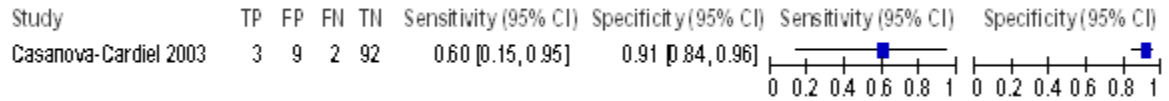
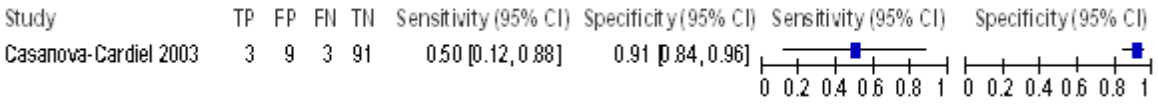
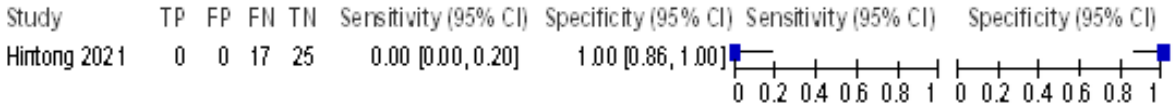


Figure 46: Sensitivity and specificity of hyperkalaemia (serum Potassium > 5 mEq/L) for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection



E.1.9 Nausea and vomiting for diagnosing adrenal insufficiency

Figure 47: Sensitivity and specificity of nausea and vomiting for diagnosing adrenal insufficiency (8am cortisol level of <3 µg/dL or a peak serum cortisol level of <18 µg/dL after a 5 µg ACTH stimulation test) in people using topical steroids



E.1.10 Nausea for diagnosing adrenal insufficiency

Figure 48: Sensitivity and specificity of nausea for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB

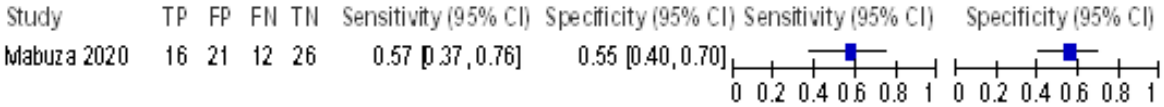
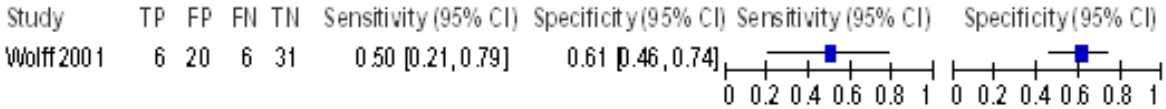


Figure 49: Sensitivity and specificity of nausea for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS



E.1.11 Vomiting for diagnosing adrenal insufficiency

Figure 50: Sensitivity and specificity of vomiting for diagnosing adrenal insufficiency (serum cortisol < 500nmol/L after low dose (1 µg/ml) short corticotropin (Synacthen®) stimulation test in people with suspected TB

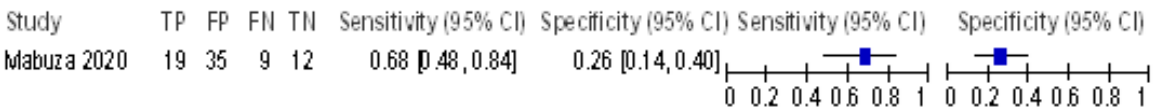


Figure 51: Sensitivity and specificity of vomiting for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test) in people with AIDS

E.1.12 Diarrhoea for diagnosing adrenal insufficiency.

Figure 52: Sensitivity and specificity of diarrhoea for diagnosing adrenal insufficiency (cortisol peak response < 11 µg after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

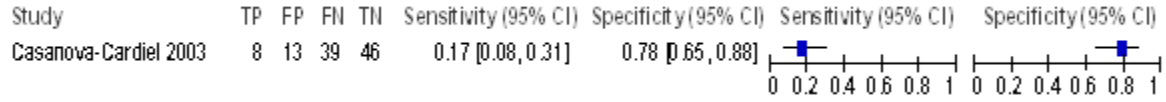


Figure 53: Sensitivity and specificity of diarrhoea for diagnosing adrenal insufficiency (twofold value of basal cortisol after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

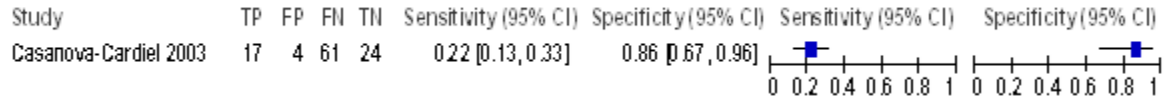


Figure 54: Sensitivity and specificity of diarrhoea for diagnosing adrenal insufficiency (any cortisol value > 18 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

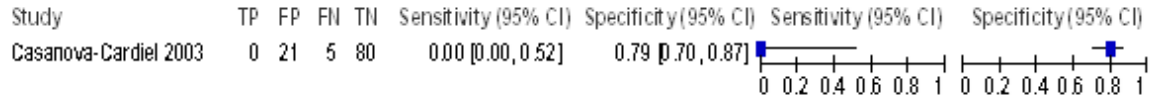


Figure 55: Sensitivity and specificity of diarrhoea for diagnosing adrenal insufficiency (any cortisol value > 20 µg/dL after low dose 10 µg short corticotropin stimulation test) in people with HIV-infection

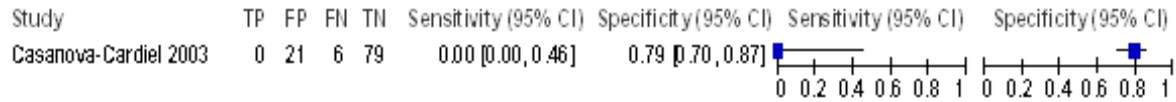
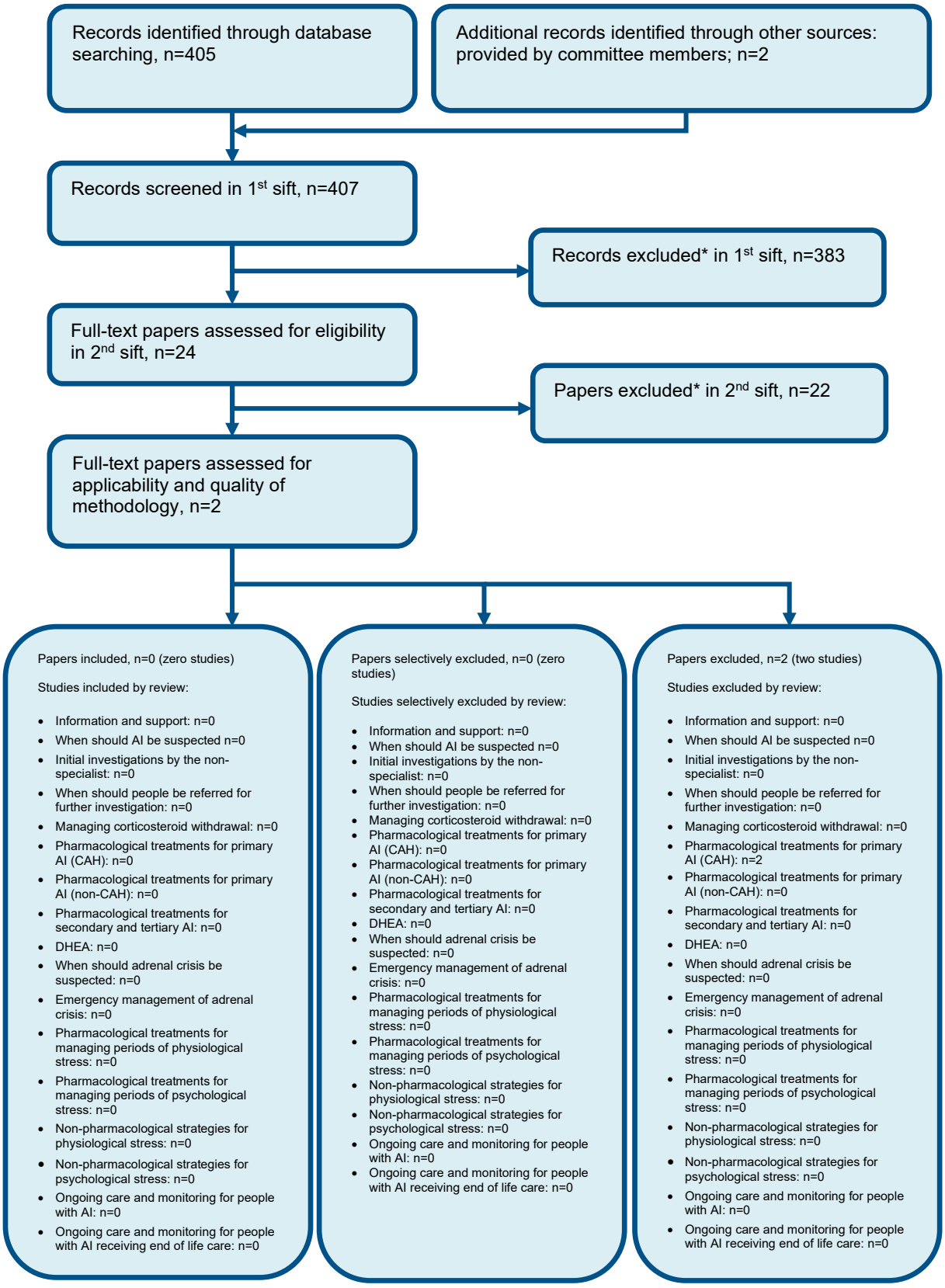


Figure 56: Sensitivity and specificity of diarrhoea for diagnosing adrenal hypofunction (all cortisol measurements <18 µg/dL including 1 µg/mL ACTH test)

Appendix F Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix G Economic evidence tables

None.

Appendix H Health economic model

No original economic modelling was undertaken for this review question.

Appendix I Excluded studies

I.1 Clinical studies

Table 16: Studies excluded from the clinical review

Study	Reason for exclusion
Abdel-Rahman, Omar; ElHalawani, Hesham; Fouad, Mona (2016) Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis. Future oncology (London, England) 12(3): 413-25	- Systematic review used as source of primary studies *Systematic review of RCTs reporting endocrine complications due to checkpoint inhibitor use e.g., hyper or hypo thyroidism and AI. 3 out of 10 studies included report AI.*
Abosmaha, E.A., Almsahli, S.E., Alsabri, S.G. et al. (2014) Coexistence of autoimmune disease with type I diabetes mellitus in Libyan patients. International Journal of Pharmacy and Pharmaceutical Sciences 6(2): 120-124	- Study does not report multivariable analysis of assessed risk factor(s)
Abu Bakar, K., Khalil, K., Lim, Y.N. et al. (2020) Adrenal Insufficiency in Children with Nephrotic Syndrome on Corticosteroid Treatment. Frontiers in Pediatrics 8: 164	- Comparator in study does not match that specified in this review protocol
Afreen, Bahjat; Khan, Khurshid Ahmed; Riaz, Amna (2017) Adrenal Insufficiency In Pakistani Hiv Infected Patients. Journal of Ayub Medical College, Abbottabad: JAMC 29(3): 428-431	- Study does not report adrenal insufficiency diagnosis or association data
Ahmet, Alexandra, Benchimol, Eric I, Goldbloom, Ellen B et al. (2016) Adrenal suppression in children treated with swallowed fluticasone and oral viscous budesonide for eosinophilic esophagitis. Allergy, asthma, and clinical immunology: official journal of the Canadian Society of Allergy and Clinical Immunology 12: 49	- Study does not report multivariable analysis of assessed risk factor(s)
Ahmet, Alexandra, Brienza, Vincent, Tran, Audrey et al. (2017) Frequency and Duration of Adrenal Suppression Following Glucocorticoid Therapy in Children With Rheumatic Diseases. Arthritis care & research 69(8): 1224-1230	- Study does not report multivariable analysis of assessed risk factor(s)
Al Argan, Reem, Ramadhan, Abdulaziz, Agnihotram, Ramanakumar V et al. (2021) Baseline MRI findings as predictors of hypopituitarism in patients with non-functioning pituitary adenomas. Endocrine connections 10(11): 1445-1454	- Study does not contain a risk factor relevant to this review protocol
Al-Aridi, Ribal; Abdelmannan, Dima; Arafah, Baha M (2011) Biochemical diagnosis of adrenal insufficiency: the added value of dehydroepiandrosterone sulfate measurements. Endocrine practice : official journal of the	- Review article but not a systematic review

Study	Reason for exclusion
American College of Endocrinology and the American Association of Clinical Endocrinologists 17(2): 261-70	
Albert, L., Profitos, J., Sanchez-Delgado, J. et al. (2019) Salivary cortisol determination in ACTH stimulation test to diagnose adrenal insufficiency in patients with liver cirrhosis. International Journal of Endocrinology 2019: 7251010	- Study does not contain any signs or symptoms relevant to this review protocol
Albert, Stewart G; Ariyan, Srividya; Rather, Ayesha (2011) The effect of etomidate on adrenal function in critical illness: a systematic review. Intensive care medicine 37(6): 901-10	- Systematic review used as source of primary studies
Ali, S.R., Bryce, J., Krone, N.P. et al. (2022) Management of Acute Adrenal Insufficiency-Related Adverse Events in Children with Congenital Adrenal Hyperplasia: Results of an International Survey of Specialist Centres. Hormone Research in Paediatrics 95(4): 363-373	- Study does not report adrenal insufficiency diagnosis or association data
Archambault, Patrick, Dionne, Clermont E, Lortie, Gilles et al. (2012) Adrenal inhibition following a single dose of etomidate in intubated traumatic brain injury victims. CJEM 14(5): 270-82	- Study does not report adrenal insufficiency diagnosis or association data
Arrington-Sanders, Renata; Hutton, Nancy; Siberry, George K (2006) Ritonavir-fluticasone interaction causing Cushing syndrome in HIV-infected children and adolescents. The Pediatric infectious disease journal 25(11): 1044-8	- Study does not report multivariable analysis of assessed risk factor(s)
Aydin, Banu Kucukemre, Saka, Nurcin, Bas, Firdevs et al. (2019) Frequency of Ambiguous Genitalia in 14,177 Newborns in Turkey. Journal of the Endocrine Society 3(6): 1185-1195	- Study does not report adrenal insufficiency diagnosis or association data
Azeez, Taoreed Adegoke, Irojah, Olakunle Ayorinde, Lakoh, Sulaiman et al. (2021) A systematic review of adrenal insufficiency among patients with pulmonary tuberculosis in Sub-Saharan Africa. International journal of mycobacteriology 10(1): 1-7	- Study does not report adrenal insufficiency diagnosis or association data - Systematic review used as source of primary studies
Bachelot, Anne, Golmard, Jean Louis, Dulon, Jerome et al. (2015) Determining clinical and biological indicators for health outcomes in adult patients with childhood onset of congenital adrenal hyperplasia. European journal of endocrinology 173(2): 175-84	- Comparator in study does not match that specified in this review protocol - Study does not contain a risk factor relevant to this review protocol
Bai, Xuefeng, Lin, Xiahong, Zheng, Kainan et al. (2020) Mapping endocrine toxicity spectrum of	- Study design not relevant to this review protocol

Study	Reason for exclusion
immune checkpoint inhibitors: a disproportionality analysis using the WHO adverse drug reaction database, VigiBase. Endocrine 69(3): 670-681	*retrospective cohort study*
Balibegloo, Maryam, Nejadghaderi, Seyed Aria, Sadeghalvad, Mona et al. (2021) Adverse events associated with immune checkpoint inhibitors in patients with breast cancer: A systematic review and meta-analysis. International immunopharmacology 96: 107796	- Systematic review used as source of primary studies
Bangsgaard, Regitze, Main, Katharina M, Boberg-Ans, Goril et al. (2018) Adrenal Suppression in Infants Treated with Topical Ocular Glucocorticoids. Ophthalmology 125(10): 1638-1643	- Study does not report multivariable analysis of assessed risk factor(s)
Barroso-Sousa, Romualdo, Barry, William T, Garrido-Castro, Ana C et al. (2018) Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. JAMA oncology 4(2): 173-182	- Study does not report adrenal insufficiency diagnosis or association data *Incidence only*
Ben-Shlomo, Anat, Mirocha, James, Gwin, Stephanie M et al. (2014) Clinical factors associated with biochemical adrenal-cortisol insufficiency in hospitalized patients. The American journal of medicine 127(8): 754-762	- Study design not relevant to this review protocol *retrospective*
Bensalah, M., Donaldson, M., Labassen, M. et al. (2020) Prevalence of hypopituitarism and quality of life in survivors of post-traumatic brain injury. Endocrinology, Diabetes and Metabolism 3(3): e00146	- Comparator in study does not match that specified in this review protocol - Study does not report multivariable analysis of assessed risk factor(s)
Bensalah, Meriem, Donaldson, Malcolm, Aribi, Yamina et al. (2018) Cortisol evaluation during the acute phase of traumatic brain injury-A prospective study. Clinical endocrinology 88(5): 627-636	- Reference standard or method of diagnosis does not match the review protocol
Bergthorsdottir, Ragnhildur, Ragnarsson, Oskar, Skrtic, Stanko et al. (2017) Visceral Fat and Novel Biomarkers of Cardiovascular Disease in Patients With Addison's Disease: A Case-Control Study. The Journal of clinical endocrinology and metabolism 102(11): 4264-4272	- Population not relevant to this review protocol *population have been diagnosed with Addison's diesase.*
Betterle, C., Rossi, A., Dalla Pria, S. et al. (1993) Premature ovarian failure: Autoimmunity and natural history. Clinical Endocrinology 39(1): 35-43	- Study does not report adrenal insufficiency diagnosis or association data

Study	Reason for exclusion
Betterle, C, Volpato, M, Rees Smith, B et al. (1997) I. Adrenal cortex and steroid 21-hydroxylase autoantibodies in adult patients with organ-specific autoimmune diseases: markers of low progression to clinical Addison's disease. The Journal of clinical endocrinology and metabolism 82(3): 932-8	- Study does not contain a risk factor relevant to this review protocol - Study does not report multivariable analysis of assessed risk factor(s)
Betterle, C, Volpato, M, Rees Smith, B et al. (1997) II. Adrenal cortex and steroid 21-hydroxylase autoantibodies in children with organ-specific autoimmune diseases: markers of high progression to clinical Addison's disease. The Journal of clinical endocrinology and metabolism 82(3): 939-42	- Study does not contain a risk factor relevant to this review protocol - Study does not report multivariable analysis of assessed risk factor(s)
Betterle, C, Zanette, F, Pedini, B et al. (1984) Clinical and subclinical organ-specific autoimmune manifestations in type 1 (insulin-dependent) diabetic patients and their first-degree relatives. Diabetologia 26(6): 431-6	- Study design not relevant to this review protocol *Case-control* - Data not reported in an extractable format or a format that can be analysed *Prevalence data only*
Bilavsky, Efraim, Dagan, Adi, Yarden-Bilavsky, Havatzelet et al. (2011) Adrenal insufficiency during physiological stress in children after kidney or liver transplantation. Pediatric transplantation 15(3): 314-20	- Study does not report adrenal insufficiency diagnosis or association data
Boots, Johannes M M, van den Ham, E C H, Christiaans, M H L et al. (2002) Risk of adrenal insufficiency with steroid maintenance therapy in renal transplantation. Transplantation proceedings 34(5): 1696-7	- Comparator in study does not match that specified in this review protocol
Borresen, Stina W, Thorgrimsen, Toke B, Jensen, Bente et al. (2020) Adrenal insufficiency in prednisolone-treated patients with polymyalgia rheumatica or giant cell arteritis-prevalence and clinical approach. Rheumatology (Oxford, England) 59(10): 2764-2773	- Study does not report multivariable analysis of assessed risk factor(s) - Study does not contain a risk factor relevant to this review protocol *Corticosteroid dose*
Bouca, Bruno, Nogueira, Andreia, Caetano, Joana et al. (2022) Clinical characteristics of polyglandular autoimmune syndromes in pediatric age: an observational study. Journal of pediatric endocrinology & metabolism: JPEM 35(4): 477-480	- Reference standard or method of diagnosis does not match the review protocol
Brennan, Vincent, Martin-Grace, Julie, Greene, Garrett et al. (2022) The Contribution of Oral and Inhaled Glucocorticoids to Adrenal Insufficiency in Asthma. The journal of allergy	- Reference standard or method of diagnosis does not match the review protocol

Study	Reason for exclusion
and clinical immunology. In practice 10(10): 2614-2623	
Broersen, Leonie H A, Pereira, Alberto M, Jorgensen, Jens Otto L et al. (2015) Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 100(6): 2171-80	- Systematic review used as source of primary studies
Brossaud, Julie, Barat, Pascal, Georges, Agnes et al. (2012) Impact of the reference values on the clinically relevant cut-offs. The example of cortisol testing in children. Clinical chemistry and laboratory medicine 50(5): 901-3	- Study does not contain any signs or symptoms relevant to this review protocol
Brown, P H, Blundell, G, Greening, A P et al. (1991) Hypothalamo-pituitary-adrenal axis suppression in asthmatics inhaling high dose corticosteroids. Respiratory medicine 85(6): 501-10	- Study design not relevant to this review protocol
Cagliani, Joaquin A, Ruhemann, Andres, Molmenti, Ernesto et al. (2021) Association between Etomidate Use for Rapid Sequence Intubation and Adrenal Insufficiency in Sepsis. Cureus 13(2): e13445	- Study does not report multivariable analysis of assessed risk factor(s) - Study design not relevant to this review protocol *Retrospective*
Cavkaytar, Ozlem, Vuralli, Dogus, Arik Yilmaz, Ebru et al. (2015) Evidence of hypothalamic-pituitary-adrenal axis suppression during moderate-to-high-dose inhaled corticosteroid use. European journal of pediatrics 174(11): 1421-31	- Study design not relevant to this review protocol
Cerina, Vatroslav, Kruljac, Ivan, Radosevic, Jelena Marinkovic et al. (2016) Diagnostic Accuracy of Perioperative Measurement of Basal Anterior Pituitary and Target Gland Hormones in Predicting Adrenal Insufficiency After Pituitary Surgery. Medicine 95(9): e2898	- Study does not contain a risk factor relevant to this review protocol
Chacko, Shireen R, Abraham, Ananth P, Asha, Hesarghatta Shyamasunder et al. (2020) Selective perioperative steroid supplementation protocol in patients undergoing endoscopic transsphenoidal surgery for pituitary adenomas. Acta neurochirurgica 162(10): 2381-2388	- Study design not relevant to this review protocol
Chan, C.; Mitchell, A.; Shorr, A. (2011) The effect of etomidate on adrenal insufficiency and mortality: A meta-analysis. Chest 140(4meetingabstract)	- Conference abstract

Study	Reason for exclusion
Chan, Chee Man; Mitchell, Anthony L; Shorr, Andrew F (2012) Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis*. Critical care medicine 40(11): 2945-53	- Systematic review used as source of primary studies
Chantzichristos, Dimitrios, Persson, Anders, Miftaraj, Mervete et al. (2019) Early Clinical Indicators of Addison Disease in Adults with Type 1 Diabetes: A Nationwide, Observational, Cohort Study. The Journal of clinical endocrinology and metabolism 104(4): 1148-1157	- Study design not relevant to this review protocol *Case-control* - Study does not report multivariable analysis of assessed risk factor(s)
Chen, Xin, Chai, Yan, Wang, Shao-Bo et al. (2020) Risk factors for corticosteroid insufficiency during the sub-acute phase of acute traumatic brain injury. Neural regeneration research 15(7): 1259-1265	- Reference standard or method of diagnosis does not match the review protocol *Dexamethasone supression*
Christensson, Camilla; Thoren, Anders; Lindberg, Bengt (2008) Safety of inhaled budesonide: clinical manifestations of systemic corticosteroid-related adverse effects. Drug safety 31(11): 965-88	- Systematic review used as source of primary studies
Clark, D J, Grove, A, Cargill, R I et al. (1996) Comparative adrenal suppression with inhaled budesonide and fluticasone propionate in adult asthmatic patients. Thorax 51(3): 262-6	- Reference standard or method of diagnosis does not match the review protocol - Study design not relevant to this review protocol *RCT*
Cohan, Pejman, Wang, Christina, McArthur, David L et al. (2005) Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Critical care medicine 33(10): 2358-66	- Reference standard or method of diagnosis does not match the review protocol
Conrad, Nathalie, Misra, Shivani, Verbakel, Jan Y et al. (2023) Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK. Lancet (London, England)	- Study does not report adrenal insufficiency diagnosis or association data
Cook, M., Pratt, G., Powell, R. et al. (2019) Therapy with Steroid-Containing Regimens in Myeloma Patients Can Result in Significantly Low Serum Cortisol Levels. Clinical Lymphoma, Myeloma and Leukemia 19(10supplement): e252	- Conference abstract
Cotton, Bryan A, Guillamondegui, Oscar D, Fleming, Sloan B et al. (2008) Increased risk of adrenal insufficiency following etomidate	- Study design not relevant to this review protocol *Retrospective registry study*

Study	Reason for exclusion
exposure in critically injured patients. Archives of surgery (Chicago, Ill.: 1960) 143(1): 62-67	
Cui, Kai, Wang, Ziqi, Zhang, Qianqian et al. (2022) Immune checkpoint inhibitors and adrenal insufficiency: a large-sample case series study. Annals of translational medicine 10(5): 251	- Study does not report adrenal insufficiency diagnosis or association data *prevalence only*
Dar, Sheeraz A, Nazir, Mudasir, Lone, Roumissa et al. (2018) Clinical Spectrum of Disorders of Sex Development: A Cross-sectional Observational Study. Indian journal of endocrinology and metabolism 22(6): 774-779	- Study does not report adrenal insufficiency diagnosis or association data
Davallow Ghajar, Ladan, Wood Heickman, Lauren K, Conaway, Mark et al. (2019) Low Risk of Adrenal Insufficiency After Use of Low- to Moderate-Potency Topical Corticosteroids for Children With Atopic Dermatitis. Clinical pediatrics 58(4): 406-412	- Systematic review used as source of primary studies
de Filette, Jeroen, Andreescu, Corina Emilia, Cools, Filip et al. (2019) A Systematic Review and Meta-Analysis of Endocrine-Related Adverse Events Associated with Immune Checkpoint Inhibitors. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 51(3): 145-156	- Study does not report adrenal insufficiency diagnosis or association data
Dellon, E.S., Falk, G.W., Lucendo, A. et al. (2021) Low Rates of Glucocorticoid-Related Adverse Effects With Long-Term Treatment Of Eosinophilic Esophagitis With Fluticasone Propionate Orally Disintegrating Tablet (Apt-1011): Results From 52 Weeks Of Exposure In A Phase 2b Trial. Gastroenterology 160(6supplement): 249	- Conference abstract
Edvardsen, Kine, Hellesen, Alexander, Husebye, Eystein S et al. (2016) Analysis of cellular and humoral immune responses against cytomegalovirus in patients with autoimmune Addison's disease. Journal of translational medicine 14: 68	- Study design not relevant to this review protocol
Edwin, Stephanie B and Walker, Pamela L (2010) Controversies surrounding the use of etomidate for rapid sequence intubation in patients with suspected sepsis. The Annals of pharmacotherapy 44(78): 1307-13	- Review article but not a systematic review
Einarsdottir, Margret J, Bankvall, Maria, Robledo-Sierra, Jairo et al. (2023) Topical clobetasol treatment for oral lichen planus can cause adrenal insufficiency. Oral diseases	- Data not reported in an extractable format or a format that can be analysed *Only reports prevalence data*

Study	Reason for exclusion
El-Maouche, Diala, Hannah-Shmouni, Fady, Mallappa, Ashwini et al. (2019) Adrenal morphology and associated comorbidities in congenital adrenal hyperplasia. Clinical endocrinology 91(2): 247-255	- Study does not report adrenal insufficiency diagnosis or association data
Elamin, Mohamed B, Murad, M Hassan, Mullan, Rebecca et al. (2008) Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and metaanalyses. The Journal of clinical endocrinology and metabolism 93(5): 1553-62	- Systematic review used as source of primary studies
Emelifeonwu, J.A., Flower, H., Loan, J. et al. (2019) Prevalence of Anterior Pituitary Dysfunction 12 months or more following Traumatic Brain Injury in Adults - A Systematic review and Meta-analysis. Journal of neurotrauma	- Systematic review used as source of primary studies
Erichsen, Martina M, Lovas, Kristian, Skinningsrud, Beate et al. (2009) Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. The Journal of clinical endocrinology and metabolism 94(12): 4882-90	- Study design not relevant to this review protocol
Ersoy, G.Z.; Erguven, M.; Yildiz, M. (2023) Factors Associated with the Development of Adrenal Insufficiency in Patients with Juvenile Idiopathic Arthritis Who Received Systemic Corticosteroids. Journal of Pediatric Research 10(1): 26-33	- Study design not relevant to this review protocol
Falorni, A. and Laureti, S. (2000) Adrenal autoimmunity and correlation with adrenal dysfunction. Endocrinologist 10(3): 145-154	- Review article but not a systematic review
Farahid, O.H., Khawaja, N., Shennak, M.M. et al. (2013) Prevalence of coeliac disease among adult patients with autoimmune hypothyroidism in Jordan. Eastern Mediterranean Health Journal 20(1): 51-55	- Study design not relevant to this review protocol
Fassnacht, Martin, Arlt, Wiebke, Bancos, Irina et al. (2016) Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the Study of Adrenal Tumors. European journal of endocrinology 175(2): g1-g34	- Study design not relevant to this review protocol
Feng, Gui-Long, Zheng, Miao-Miao, Yao, Shi-Hong et al. (2021) Risk factors and predictive model of adrenocortical insufficiency in patients	- Reference standard or method of diagnosis does not match the review protocol

Study	Reason for exclusion
with traumatic brain injury. World journal of emergency medicine 12(3): 179-184	
Ferguson, A, Campieri, M, Doe, W et al. (1998) Oral budesonide as maintenance therapy in Crohn's disease--results of a 12-month study. Global Budesonide Study Group. Alimentary pharmacology & therapeutics 12(2): 175-83	- Study design not relevant to this review protocol *RCT*
Findling, J W, Buggy, B P, Gilson, I H et al. (1994) Longitudinal evaluation of adrenocortical function in patients infected with the human immunodeficiency virus. The Journal of clinical endocrinology and metabolism 79(4): 1091-6	- Data not reported in an extractable format or a format that can be analysed - Study does not report multivariable analysis of assessed risk factor(s)
Foisy, M M, Yakiwchuk, E M K, Chiu, I et al. (2008) Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV medicine 9(6): 389-96	- Review article but not a systematic review
Friedly, J.L., Comstock, B.A., Standaert, C.J. et al. (2016) Patient and procedural risk factors for cortisol suppression following epidural steroid injections for spinal stenosis. PM and R 8(9supplement): 159-s160	- Conference abstract
Gao, J., Jiao, X., Dang, Y. et al. (2017) Identification of patients with primary ovarian insufficiency caused by autoimmunity. Reproductive BioMedicine Online 35(4): 475-479	- Study does not report multivariable analysis of assessed risk factor(s)
Gleicher, Norbert, Kushnir, Vitaly A, Weghofer, Andrea et al. (2016) The importance of adrenal hypoandrogenism in infertile women with low functional ovarian reserve: a case study of associated adrenal insufficiency. Reproductive biology and endocrinology: RB&E 14: 23	- Study design not relevant to this review protocol
Gray, T.F., Borstelmann, N., Rosenberg, S. et al. (2021) Relative risk of variousendocrinopathies associated with the use of chemoimmunotherapy for triple-negative breast cancer: Asystematic review and meta-analysis. Cancer Research 81(4suppl)	- Conference abstract
Grouthier, V., Lebrun-Vignes, B., Moey, M. et al. (2020) Immune Checkpoint Inhibitors Associated Primary Adrenal Insufficiency: WHO VigiBase Report Analysis. The oncologist	- Study design not relevant to this review protocol
Grouthier, Virginie, Lebrun-Vignes, Benedicte, Moey, Melissa et al. (2020) Immune Checkpoint Inhibitor-Associated Primary Adrenal	- Study does not report adrenal insufficiency diagnosis or association data

Study	Reason for exclusion
Insufficiency: WHO VigiBase Report Analysis. The oncologist 25(8): 696-701	
Guven, Ayla (2020) Different Potent Glucocorticoids, Different Routes of Exposure but the Same Result: Iatrogenic Cushing's Syndrome and Adrenal Insufficiency. Journal of clinical research in pediatric endocrinology 12(4): 383-392	- Study design not relevant to this review protocol *Retrospective case series* - Study does not report adrenal insufficiency diagnosis or association data
Haddad, Amir, Ashkenazi, Ron Ilan, Bitterman, Haim et al. (2017) Endocrine Comorbidities in Patients with Psoriatic Arthritis: A Population-based Case-controlled Study. The Journal of rheumatology 44(6): 786-790	- Study does not contain a risk factor relevant to this review protocol
Han, Hye Sook, Park, Ji Chan, Park, Suk Young et al. (2015) A Prospective Multicenter Study Evaluating Secondary Adrenal Suppression After Antiemetic Dexamethasone Therapy in Cancer Patients Receiving Chemotherapy: A Korean Southwest Oncology Group Study. The oncologist 20(12): 1432-9	- Study does not contain a risk factor relevant to this review protocol
Harel, Shira, Hursh, Brenden E, Chan, Edmond S et al. (2015) Adrenal Suppression in Children Treated with Oral Viscous Budesonide for Eosinophilic Esophagitis. Journal of pediatric gastroenterology and nutrition 61(2): 190-3	- Study design not relevant to this review protocol - Study does not report multivariable analysis of assessed risk factor(s)
Hasegawa, Shiori, Ikesue, Hiroaki, Nakao, Satoshi et al. (2020) Analysis of immune-related adverse events caused by immune checkpoint inhibitors using the Japanese Adverse Drug Event Report database. Pharmacoepidemiology and drug safety 29(10): 1279-1294	- Study does not report adrenal insufficiency diagnosis or association data
Heckmann, M, Wudy, S A, Haack, D et al. (2000) Serum cortisol concentrations in ill preterm infants less than 30 weeks gestational age. Acta paediatrica (Oslo, Norway: 1992) 89(9): 1098-103	- Reference standard or method of diagnosis does not match the review protocol
Hildreth, Amy N, Mejia, Vicente A, Maxwell, Robert A et al. (2008) Adrenal suppression following a single dose of etomidate for rapid sequence induction: a prospective randomized study. The Journal of trauma 65(3): 573-9	- Study does not report adrenal insufficiency diagnosis or association data
Holme, J, Tomlinson, J W, Stockley, R A et al. (2008) Adrenal suppression in bronchiectasis and the impact of inhaled corticosteroids. The European respiratory journal 32(4): 1047-52	- Study does not report multivariable analysis of assessed risk factor(s)
Hou, X., Xu, X., Chen, X. et al. (2019) Analysis of clinical manifestations and gene mutations in	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
infants with 21-hydroxylase deficiencies. International Journal of Clinical and Experimental Medicine 12(5): 5373-5380	
Hoyos-Martinez, Alfonso, Horne, Vincent E, Wood, Alexis C et al. (2021) Prevalence of Adrenal Insufficiency and Glucocorticoid Use in Pediatric Pseudotumor Cerebri Syndrome. Journal of neuro-ophthalmology: the official journal of the North American Neuro-Ophthalmology Society 41(4): e451-e457	- Study design not relevant to this review protocol
Huber, Benedikt M, Bolt, Isabel B, Sauvain, Marie-Josephe et al. (2010) Adrenal insufficiency after glucocorticoid withdrawal in children with rheumatic diseases. Acta paediatrica (Oslo, Norway: 1992) 99(12): 1889-93	- Study does not report adrenal insufficiency diagnosis or association data
Iglesias, Pedro; Sanchez, Juan Cristobal; Diez, Juan Jose (2021) Isolated ACTH deficiency induced by cancer immunotherapy: a systematic review. Pituitary 24(4): 630-643	- Systematic review used as source of primary studies
Imrich, R, Vlcek, M, Kerlik, J et al. (2014) Determinants of adrenal androgen hypofunction in premenopausal females with rheumatoid arthritis. Physiological research 63(3): 321-9	- Study does not report multivariable analysis of assessed risk factor(s)
Iribarren, Jose L, Jimenez, Juan J, Hernandez, Domingo et al. (2010) Relative adrenal insufficiency and hemodynamic status in cardiopulmonary bypass surgery patients. A prospective cohort study. Journal of cardiothoracic surgery 5: 26	- Reference standard or method of diagnosis does not match the review protocol
Iwanaga, K., Yamamoto, A., Matsukura, T. et al. (2017) Corticotrophin-releasing hormone stimulation tests for the infants with relative adrenal insufficiency. Clinical Endocrinology 87(6): 660-664	- Study does not report adrenal insufficiency diagnosis or association data
Izzy, Saef, Chen, Patrick M, Tahir, Zabreen et al. (2022) Association of Traumatic Brain Injury with the Risk of Developing Chronic Cardiovascular, Endocrine, Neurological, and Psychiatric Disorders. JAMA network open 5(4): e229478	- Reference standard or method of diagnosis does not match the review protocol
Jahan, N.; Rehman, S.; Tijani, L. (2022) The relative risk of various endocrinopathies associated with neoadjuvant chemoimmunotherapy use in early-stage triple-negative breast cancer: A systematic review and meta-analysis. Cancer Research 82(4suppl)	- Conference abstract

Study	Reason for exclusion
Joseph, Rebecca M, Hunter, Ann Louise, Ray, David W et al. (2016) Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. Seminars in arthritis and rheumatism 46(1): 133-41	- Systematic review used as source of primary studies
Kachroo, P., Stewart, I.D., Kelly, R.S. et al. (2022) Metabolomic profiling reveals extensive adrenal suppression due to inhaled corticosteroid therapy in asthma. Nature Medicine 28(4): 814-822	- Study does not report adrenal insufficiency diagnosis or association data
Kakarla, V., Balagopal, M., Shaik, N.R. et al. (2022) A Study Of Prevalence Of Thyroid Dysfunction In Type 1 Diabetic Children In A Tertiary Care Hospital From A Sub-Urban Population. Journal of Pharmaceutical Negative Results 13: 2244-2246	- Reference standard or method of diagnosis does not match the review protocol
Kanji, S., Morin, S., Agtarap, K. et al. (2022) Adverse Events Associated with Immune Checkpoint Inhibitors: Overview of Systematic Reviews. Drugs 82(7): 793-809	- Systematic review used as source of primary studies
Kaplan, S.A. (1979) Disorders of the adrenal cortex. I. Pediatric Clinics of North America 26(1): 65-76	- Review article but not a systematic review
Karaguzel, Gulay, Atay, Suleyman, Deger, Orhan et al. (2012) The effects of three specific conditions related to critical care on adrenal function in children. Intensive care medicine 38(10): 1689-96	- Study does not report adrenal insufficiency diagnosis or association data
Killeen, A.A., Hanson, N.Q., Eklund, R. et al. (1992) Prevalence of nonclassical congenital adrenal hyperplasia among women self-referred for electrolytic treatment of hirsutism. American Journal of Medical Genetics 42(2): 197-200	- Study does not report adrenal insufficiency diagnosis or association data
Kim, Tae Yun, Rhee, Joong Eui, Kim, Kyu Seok et al. (2008) Etomidate should be used carefully for emergent endotracheal intubation in patients with septic shock. Journal of Korean medical science 23(6): 988-91	- Study design not relevant to this review protocol
Kopacek, Cristiane, Prado, Mayara J, da Silva, Claudia M D et al. (2019) Clinical and molecular profile of newborns with confirmed or suspicious congenital adrenal hyperplasia detected after a public screening program implementation. Jornal de pediatria 95(3): 282-290	- Study does not report adrenal insufficiency diagnosis or association data
Kromah, Fatuma, Tyroch, Alan, McLean, Susan et al. (2011) Relative adrenal insufficiency in the critical care setting: debunking the classic myth. World journal of surgery 35(8): 1818-23	- Reference standard or method of diagnosis does not match the review protocol

Study	Reason for exclusion
Kronvall, Erik, Sonesson, Bengt, Valdemarsson, Stig et al. (2016) Reduced Quality of Life in Patients with Pituitary Dysfunction After Aneurysmal Subarachnoid Hemorrhage: A Prospective Longitudinal Study. World neurosurgery 88: 83-91	- Study does not report adrenal insufficiency diagnosis or association data
Kuenzig, M Ellen, Rezaie, Ali, Seow, Cynthia H et al. (2014) Budesonide for maintenance of remission in Crohn's disease. The Cochrane database of systematic reviews: cd002913	- Systematic review used as source of primary studies
Kurokawa, Kana, Mitsuishi, Yoichiro, Shimada, Naoko et al. (2023) Clinical characteristics of adrenal insufficiency induced by pembrolizumab in non-small-cell lung cancer. Thoracic cancer 14(5): 442-449	- Study does not report adrenal insufficiency diagnosis or association data - Study design not relevant to this review protocol *Retrospective*
Kwda, Anuradha, Gldc, Prematilake, Baui, Batuwita et al. (2019) Effect of long-term inhaled corticosteroid therapy on adrenal suppression, growth and bone health in children with asthma. BMC pediatrics 19(1): 411	- Study does not report multivariable analysis of assessed risk factor(s) - Study does not contain any signs or symptoms relevant to this review protocol - Study does not contain a risk factor relevant to this review protocol *Dose and duration of corticosteroid use analysed as diagnostic factors.*
Kwon, Min Kwan, Kim, Junhwan, Ahn, Jonghwa et al. (2022) Clinical Features and Risk Factors of Adrenal Insufficiency in Patients with Cancer Admitted to the Hospitalist-Managed Medical Unit. Journal of Korean medical science 37(28): e222	- Study design not relevant to this review protocol *retrospective*
Kwon, Yong Soo, Kang, Eunhae, Suh, Gee Young et al. (2009) A prospective study on the incidence and predictive factors of relative adrenal insufficiency in Korean critically ill patients. Journal of Korean medical science 24(4): 668-73	- Study does not contain a risk factor relevant to this review protocol
Lapi, Francesco, Kezouh, Abbas, Suissa, Samy et al. (2013) The use of inhaled corticosteroids and the risk of adrenal insufficiency. The European respiratory journal 42(1): 79-86	- Reference standard or method of diagnosis does not match the review protocol
Lee, Keum Hwa, Lee, HyunJeong, Lee, Cheol-Hun et al. (2019) Adrenal insufficiency in systematic lupus erythematosus (SLE) and antiphospholipid syndrome (APS): A systematic review. Autoimmunity reviews 18(1): 1-8	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
Lichtenstein, G R, Bengtsson, B, Hapten-White, L et al. (2009) Oral budesonide for maintenance of remission of Crohn's disease: a pooled safety analysis. Alimentary pharmacology & therapeutics 29(6): 643-53	- Study design not relevant to this review protocol
Lipworth, B J (1999) Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. Archives of internal medicine 159(9): 941-55	- Comparator in study does not match that specified in this review protocol *Compares different corticosteroids with each other.* - Reference standard or method of diagnosis does not match the review protocol *Association with cortisol levels as a continuous variable (no diagnostic threshold used)*
Lobatto, D.J., de Vries, F., Zamanipoor Najafabadi, A.H. et al. (2018) Preoperative risk factors for postoperative complications in endoscopic pituitary surgery: a systematic review. Pituitary 21(1): 84-97	- Systematic review used as source of primary studies
Lomenick, Jefferson P, Reifschneider, Kent L, Lucky, Anne W et al. (2009) Prevalence of adrenal insufficiency following systemic glucocorticoid therapy in infants with hemangiomas. Archives of dermatology 145(3): 262-6	- Study does not report multivariable analysis of assessed risk factor(s)
Lugogo, Njira, Chipps, Bradley E, Panettieri, Reynold A Jr et al. (2022) Long-Term Use of Maintenance Systemic Corticosteroids is Associated with Multiple Adverse Conditions in a Large, Real-World Cohort of US Adults with Severe Asthma. Journal of asthma and allergy 15: 1753-1761	- Study design not relevant to this review protocol *retrospective: definition of AI not stated and derived from medical records.*
Makimattila, S., Harjutsalo, V., Forsblom, C. et al. (2020) Every fifth individual with type 1 diabetes suffers from an additional autoimmune disease: A Finnish nationwide study. Diabetes Care 43(5): 1041-1047	- Study design not relevant to this review protocol
Malerba, Gabriel, Romano-Girard, Florence, Cravoisy, Aurelie et al. (2005) Risk factors of relative adrenocortical deficiency in intensive care patients needing mechanical ventilation. Intensive care medicine 31(3): 388-92	- Study does not report adrenal insufficiency diagnosis or association data *Reports on relative adrenocortical deficiency based on high dose corticotropin test.*
Manglik, Savita, Flores, Eugene, Lubarsky, Laura et al. (2003) Glucocorticoid insufficiency in patients who present to the hospital with severe sepsis: a prospective clinical trial. Critical care medicine 31(6): 1668-75	- Data not reported in an extractable format or a format that can be analysed

Study	Reason for exclusion
Manosroi, Worapaka, Phimphilai, Mattabhorn, Khorana, Jiraporn et al. (2020) Predictive Factors of Adrenal Insufficiency in Outpatients with Indeterminate Serum Cortisol Levels: A Retrospective Study. Medicina (Kaunas, Lithuania) 56(1)	- Study design not relevant to this review protocol *Retrospective cohort*
Manosroi, Worapaka, Pipanmekaporn, Tanyong, Khorana, Jiraporn et al. (2021) A Predictive Risk Score to Diagnose Adrenal Insufficiency in Outpatients: A 7 Year Retrospective Cohort Study. Medicines (Basel, Switzerland) 8(3)	- Study design not relevant to this review protocol *retrospective cohort study*
Mansoor, S., Baloch, M.H., Khan, Z. et al. (2023) A clinical account of Pakistani children suffering from congenital adrenal hyperplasia. Journal of the Pakistan Medical Association 73(2): 366-369	- Study design not relevant to this review protocol
Mantan, M, Grover, R, Kaushik, S et al. (2018) Adrenocortical Suppression in Children with Nephrotic Syndrome Treated with Low-Dose Alternate Day Corticosteroids. Indian journal of nephrology 28(3): 203-208	- Study does not report adrenal insufficiency diagnosis or association data *Correlation data only*
Mantilla, E.C., Abramowitz, J., Dan, T. et al. (2020) Prolonged steroid dependence in adult patients with glioma. Anticancer Research 40(4): 2059-2064	- Study design not relevant to this review protocol
Matsubayashi, Sunao; Nakatake, Nobuhiro; Hara, Takeshi (2020) Possible adrenal insufficiency among fatigue patients in a psychosomatic medical clinic. Endocrine journal 67(1): 53-57	- Study does not report multivariable analysis of assessed risk factor(s)
Mattour, A.H., Janakiraman, N., Farhan, S. et al. (2015) Incidence of adrenal insufficiency in patients with multiple myeloma during high dose chemotherapy and autologous stem cell transplant. Biology of Blood and Marrow Transplantation 21(2suppl1): 142	- Conference abstract
McKenna, D S, Wittber, G M, Nagaraja, H N et al. (2000) The effects of repeat doses of antenatal corticosteroids on maternal adrenal function. American journal of obstetrics and gynecology 183(3): 669-73	- Data not reported in an extractable format or a format that can be analysed
Mebrahtu, Teumzghi F, Morgan, Ann W, Keeley, Adam et al. (2019) Dose Dependency of Iatrogenic Glucocorticoid Excess and Adrenal Insufficiency and Mortality: A Cohort Study in England. The Journal of clinical endocrinology and metabolism 104(9): 3757-3767	- Study does not contain a risk factor relevant to this review protocol *GC dose* - Study design not relevant to this review protocol

Study	Reason for exclusion
	retrospective
Menon, Kusum, Ward, Roxanne E, Lawson, Margaret L et al. (2010) A prospective multicenter study of adrenal function in critically ill children. American journal of respiratory and critical care medicine 182(2): 246-51	- Study does not contain a risk factor relevant to this review protocol
Methiniti, D., Hamilton, J., Saravanan, V. et al. (2009) Consider hypoadrenalism in patients with fatigue and rheumatic disease. Rheumatology 48(suppl1): i113	- Conference abstract
Meya, David B, Katabira, Elly, Otim, Marcel et al. (2007) Functional adrenal insufficiency among critically ill patients with human immunodeficiency virus in a resource-limited setting. African health sciences 7(2): 101-7	- Reference standard or method of diagnosis does not match the review protocol
Mourinho Bala, Nadia, Goncalves, Raquel S, Serra Caetano, Joana et al. (2022) Autoimmune Primary Adrenal Insufficiency in Children. Journal of clinical research in pediatric endocrinology 14(3): 308-312	- Population not relevant to this review protocol *All had adrenal insufficiency.* - Study does not report multivariable analysis of assessed risk factor(s) - Study does not report adrenal insufficiency diagnosis or association data
Muller, M, Beiglbock, H, Fellinger, P et al. (2021) Micro- and macrovascular function in patients suffering from primary adrenal insufficiency: a cross-sectional case-control study. Journal of endocrinological investigation 44(2): 339-345	- Study design not relevant to this review protocol *case-control* - Study does not contain a risk factor relevant to this review protocol
Mytareli, Chrysoula, Ziogas, Dimitrios C, Karampela, Athina et al. (2023) The Uncharted Landscape of Rare Endocrine Immune-Related Adverse Events. Cancers 15(7)	- Systematic review used as source of primary studies
Naggirinya, Agnes Bwanika, Mujugira, Andrew, Meya, David B et al. (2020) Functional adrenal insufficiency among tuberculosis-human immunodeficiency virus co-infected patients: a cross-sectional study in Uganda. BMC research notes 13(1): 224	- Study does not contain a risk factor relevant to this review protocol
Nederstigt, C, Uitbeijerse, B S, Janssen, L G M et al. (2019) Associated auto-immune disease in type 1 diabetes patients: a systematic review and meta-analysis. European journal of endocrinology 180(2): 135-144	- Systematic review used as source of primary studies
Neogi, Subhasis, Mukhopadhyay, Pradip, Sarkar, Niladri et al. (2021) Overt and	- Data not reported in an extractable format or a format that can be analysed

Study	Reason for exclusion
Subclinical Adrenal Insufficiency in Pulmonary Tuberculosis. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 27(6): 601-606	
Ng, P C, Fok, T F, Wong, G W et al. (1998) Pituitary-adrenal suppression in preterm, very low birth weight infants after inhaled fluticasone propionate treatment. The Journal of clinical endocrinology and metabolism 83(7): 2390-3	- Study design not relevant to this review protocol
Ng, P C, Lee, C H, Lam, C W K et al. (2004) Transient adrenocortical insufficiency of prematurity and systemic hypotension in very low birthweight infants. Archives of disease in childhood. Fetal and neonatal edition 89(2): f119-26	- Reference standard or method of diagnosis does not match the review protocol
Nie, Ding, Fang, Qiuyue, Wong, Wakam et al. (2023) The effect of endoscopic transsphenoidal somatotroph tumors resection on pituitary hormones: systematic review and meta-analysis. World journal of surgical oncology 21(1): 71	- Systematic review used as source of primary studies
Oboni, Jean-Baptiste, Marques-Vidal, Pedro, Pralong, Francois et al. (2013) Predictive factors of adrenal insufficiency in patients admitted to acute medical wards: a case control study. BMC endocrine disorders 13: 3	- Study design not relevant to this review protocol *retrospective design*
Odeniyi, I A, Fasanmade, O A, Ajala, M O et al. (2013) Adrenocortical function in Nigerians with human immunodeficiency virus infection. Ghana medical journal 47(4): 171-7	- Study design not relevant to this review protocol
Oyama, T and Takiguchi, M (1972) Prediction of adrenal hypofunction in anaesthesia. Canadian Anaesthetists' Society journal 19(3): 239-50	- Data not reported in an extractable format or a format that can be analysed
Park, JungHyun, Kwak, Jueun, Chung, Sukyung et al. (2020) Incidence of Adrenal Insufficiency and Cushing's Syndrome After Long-Term Epidural Steroid Injections Over Six Months or Longer: A Preliminary Study. Journal of pain research 13: 1505-1514	- Study does not report multivariable analysis of assessed risk factor(s) - Study does not contain a risk factor relevant to this review protocol
Park, Sang Hoon, Joo, Min Sun, Kim, Byoung Hoon et al. (2018) Clinical characteristics and prevalence of adrenal insufficiency in hemodynamically stable patients with cirrhosis. Medicine 97(26): e11046	- Study does not contain a risk factor relevant to this review protocol - Study does not report multivariable analysis of assessed risk factor(s) *undertaken but not reported.*

Study	Reason for exclusion
Pei, Wen-Guang, Chen, Wen-Zheng, Wu, Yu-Kang et al. (2023) Immune-related adverse events associated with immune checkpoint inhibitors for advanced gastric and gastroesophageal junction cancer: A meta-analysis. World journal of gastrointestinal oncology 15(2): 352-367	- Systematic review used as source of primary studies
Philla, Katherine Q, Min, Steve B, Hefner, Jody N et al. (2015) Swallowed glucocorticoid therapy for eosinophilic esophagitis in children does not suppress adrenal function. Journal of pediatric endocrinology & metabolism: JPEM 28(910): 1101-6	- Study does not report adrenal insufficiency diagnosis or association data
Philpott, H., Reed, C.C., Dougherty, M. et al. (2017) Adrenal insufficiency is rare with topical corticosteroid treatment for eosinophilic esophagitis: A systematic review. American Journal of Gastroenterology 112(supplement1): 193-s194	- Systematic review used as source of primary studies
Piedrola, G, Casado, J L, Lopez, E et al. (1996) Clinical features of adrenal insufficiency in patients with acquired immunodeficiency syndrome. Clinical endocrinology 45(1): 97-101	- Study design not relevant to this review protocol
Preville-Ratelle, Sebastien, Coriati, Adele, Menard, Aurelie et al. (2018) Adrenal Insufficiency in Cystic Fibrosis: A Rare Phenomenon?. Canadian respiratory journal 2018: 3629031	- Study design not relevant to this review protocol *retrospective* - Study does not report multivariable analysis of assessed risk factor(s)
Raschi, Emanuel, Mazzarella, Alessandra, Antonazzo, Ippazio Cosimo et al. (2019) Toxicities with Immune Checkpoint Inhibitors: Emerging Priorities From Disproportionality Analysis of the FDA Adverse Event Reporting System. Targeted oncology 14(2): 205-221	- Study design not relevant to this review protocol
Reddy, Pramod (2021) Diagnosis and Management of Adrenal Insufficiency in Hospitalized Patients. American journal of therapeutics 28(2): e238-e244	- Review article but not a systematic review
Rensen, Niki, Gemke, Reinoud Jbj, van Dalen, Elvira C et al. (2017) Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. The Cochrane database of systematic reviews 11: cd008727	- Systematic review used as source of primary studies
Rezaie, Ali, Kuenzig, M Ellen, Benchimol, Eric I et al. (2015) Budesonide for induction of	- Systematic review used as source of primary studies

Study	Reason for exclusion
remission in Crohn's disease. The Cochrane database of systematic reviews: cd000296	
Rodriguez-Gutierrez, Rene, Gonzalez-Velazquez, Camilo, Gonzalez-Saldivar, Gerardo et al. (2014) Glucocorticoid functional reserve in full-spectrum intensity of primary hypothyroidism. International journal of endocrinology 2014: 313519	- Study does not report multivariable analysis of assessed risk factor(s)
Ross, Ian Louis and Levitt, Naomi S (2013) Addison's disease symptoms--a cross sectional study in urban South Africa. PloS one 8(1): e53526	- Study design not relevant to this review protocol
Saari, Viivi, Holopainen, Elina, Makitie, Outi et al. (2020) Pubertal development and premature ovarian insufficiency in patients with APECED. European journal of endocrinology 183(5): 513-520	- Study does not report target condition
Sadeghi, P., Aghighi, Y., Ziaee, V. et al. (2019) Adrenal insufficiency in children with juvenile idiopathic arthritis (JIA) treated with prednisolone. Journal of Comprehensive Pediatrics 10(2): e64681	- Data not reported in an extractable format or a format that can be analysed - Study does not report multivariable analysis of assessed risk factor(s)
Sahlander, F, Patrova, J, Mannheimer, B et al. (2023) Congenital adrenal hyperplasia in patients with adrenal tumors: a population-based case-control study. Journal of endocrinological investigation 46(3): 559-565	- Study design not relevant to this review protocol *retrospective cohort study and no MV analysis*
Sakao, Yukitoshi, Sugiura, Takeshi, Tsuji, Takayuki et al. (2014) Clinical manifestation of hypercalcemia caused by adrenal insufficiency in hemodialysis patients: a case-series study. Internal medicine (Tokyo, Japan) 53(14): 1485-90	- Study design not relevant to this review protocol
Sakar, M., Ozdogan, S., Ucar, A. et al. (2019) The prevalence of hypothalamic-pituitary-adrenal axis suppression in children with persistent asthma. Iranian Journal of Pediatrics 29(5): e90891	- Study does not contain any signs or symptoms relevant to this review protocol
Saleem, Mohammed D and Feldman, Steven R (2018) Desoximetasone 0.25% spray, adrenal suppression and efficacy in extensive plaque psoriasis. The Journal of dermatological treatment 29(1): 36-38	- Comparator in study does not match that specified in this review protocol
Salgado, D R; Rocco, J R; Rosso Verdeal, J C (2008) Adrenal function in different subgroups of septic shock patients. Acta anaesthesiologica Scandinavica 52(1): 36-44	- Study does not report target condition

Study	Reason for exclusion
Sampieri, Gianluca, Namavarian, Amirpouyan, Lee, John J W et al. (2022) Hypothalamic-pituitary-adrenal axis suppression and intranasal corticosteroid use: A systematic review and meta-analysis. International forum of allergy & rhinology 12(1): 11-27	- Study does not report adrenal insufficiency diagnosis or association data *Prevalence data only*
Sarna, S, Hoppu, K, Neuvonen, P J et al. (1997) Methylprednisolone exposure, rather than dose, predicts adrenal suppression and growth inhibition in children with liver and renal transplants. The Journal of clinical endocrinology and metabolism 82(1): 75-7	- Reference standard or method of diagnosis does not match the review protocol
Schmidt, Diana C, Kessel, Line, Bach-Holm, Daniella et al. (2023) Prevalence and risk factors for hypothalamus-pituitary-adrenal axis suppression in infants receiving glucocorticoid eye drops after ocular surgery. Acta ophthalmologica 101(2): 229-235	- Study does not report multivariable analysis of assessed risk factor(s) - Study does not contain a risk factor relevant to this review protocol
Schonfeld, Sara J, Tucker, Margaret A, Engels, Eric A et al. (2022) Immune-Related Adverse Events After Immune Checkpoint Inhibitors for Melanoma Among Older Adults. JAMA network open 5(3): e223461	- Study design not relevant to this review protocol *retrospective and diagnosis based on medical claims database terms.*
Shah, Koral, Boyd, Jennifer W, Broussard, Julia R et al. (2022) Adrenocortical Function in Children With Brain Tumors and Pediatric Hematopoietic Cell Transplantation Recipients. Journal of pediatric hematology/oncology 44(2): e469-e473	- Study does not report multivariable analysis of assessed risk factor(s)
Sharma, Neera, Sharma, Lokesh Kumar, Anand, Atul et al. (2018) Presence, patterns & predictors of hypocortisolism in patients with HIV infection in India. The Indian journal of medical research 147(2): 142-150	- Study does not report multivariable analysis of assessed risk factor(s)
Sherlock, Mary E, MacDonald, John K, Griffiths, Anne Marie et al. (2015) Oral budesonide for induction of remission in ulcerative colitis. The Cochrane database of systematic reviews: cd007698	- Systematic review used as source of primary studies
Shi, Yun, Shen, Min, Zheng, Xuqin et al. (2021) Immune Checkpoint Inhibitor-Induced Adrenalitis and Primary Adrenal Insufficiency: Systematic Review and Optimal Management. Endocrine practice: official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 27(2): 165-169	- Study design not relevant to this review protocol *Systematic review of case reports*
Shin, Won Shik, Ahn, Dong Ki, Kim, Myung Jin et al. (2019) Influence of Epidural Steroid	- Study design not relevant to this review protocol

Study	Reason for exclusion
Injection on Adrenal Function. Clinics in orthopedic surgery 11(2): 183-186	*retrospective* - Study does not contain a risk factor relevant to this review protocol *spinal surgery*
Simon, Albane, Warszawski, Josiane, Kariyawasam, Dulanjalee et al. (2011) Association of prenatal and postnatal exposure to lopinavir-ritonavir and adrenal dysfunction among uninfected infants of HIV-infected mothers. JAMA 306(1): 70-8	- Reference standard or method of diagnosis does not match the review protocol
Singhal, Mukul, Sharma, Shrikant, Tom, Nikhil Basil et al. (2022) A Study of Adrenal Insufficiency in Hemodynamically Stable Patients with Cirrhosis. The Journal of the Association of Physicians of India 70(4): 11-12	- Conference abstract
Skoll, Amanda, Boutin, Amelie, Bujold, Emmanuel et al. (2018) No. 364-Antenatal Corticosteroid Therapy for Improving Neonatal Outcomes. Journal of obstetrics and gynaecology Canada: JOGC = Journal d'obstetrique et gynecologie du Canada: JOGC 40(9): 1219-1239	- Study design not relevant to this review protocol
Skov, Inge Raadal, Madsen, Hanne, Henriksen, Daniel Pilsgaard et al. (2022) Low-dose oral corticosteroids in asthma associates with increased morbidity and mortality. The European respiratory journal 60(3)	- Reference standard or method of diagnosis does not match the review protocol *hospital given diagnosis, no further information.*
Skov, M, Main, K M, Sillesen, I B et al. (2002) Iatrogenic adrenal insufficiency as a side-effect of combined treatment of itraconazole and budesonide. The European respiratory journal 20(1): 127-33	- Study does not report multivariable analysis of assessed risk factor(s) *No association data reported.*
Smith, Ryan W, Downey, Kim, Gordon, Michelle et al. (2012) Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid. Paediatrics & child health 17(5): e34-9	- Study does not contain a risk factor relevant to this review protocol
Sridhar, Subbiah, Balachandran, Karthik, Nazirudeen, Roshan et al. (2022) Clinical Profile of Addison's Disease in a Tertiary Care Institute, Southern India - The Changing Landscape. Indian journal of endocrinology and metabolism 26(1): 50-54	- Study does not report adrenal insufficiency diagnosis or association data *prevalence data only* - Study design not relevant to this review protocol *Retrospective*
Staby, Ida, Krogh, Jesper, Klose, Marianne et al. (2021) Pituitary function after transsphenoidal surgery including measurement	- Study does not contain a risk factor relevant to this review protocol

Study	Reason for exclusion
of basal morning cortisol as predictor of adrenal insufficiency. Endocrine connections 10(7): 750-757	- Study does not contain any signs or symptoms relevant to this review protocol
Tallis, Philippa H, Rushworth, R Louise, Torpy, David J et al. (2019) Adrenal insufficiency due to bilateral adrenal metastases - A systematic review and meta-analysis. Heliyon 5(5): e01783	- Systematic review used as source of primary studies *Included case reports and case series as well as comparative studies.* - Study does not report adrenal insufficiency diagnosis or association data *Prevalence and correlation data only*
Thorp, J A, Jones, A M, Hunt, C et al. (2001) The effect of multidose antenatal betamethasone on maternal and infant outcomes. American journal of obstetrics and gynecology 184(2): 196-202	- Reference standard or method of diagnosis does not match the review protocol
Toniutto, Pierluigi, Fabris, Carlo, Fumolo, Elisa et al. (2008) Prevalence and risk factors for delayed adrenal insufficiency after liver transplantation. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society 14(7): 1014-9	- Study does not report target condition
Turmel-Roy, Justine, Bedard, Marc-Antoine, Millette, Maude et al. (2020) Risk of adrenal insufficiency following intra-articular or periarticular corticosteroid injections among children with chronic arthritis. Journal of pediatric endocrinology & metabolism: JPEM 33(10): 1257-1263	- Study design not relevant to this review protocol
Valentin, Amalie, Borresen, Stina Willemoes, Rix, Marianne et al. (2020) Adrenal insufficiency in kidney transplant patients during low-dose prednisolone therapy: a cross-sectional case-control study. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association 35(12): 2191-2197	- Study does not report multivariable analysis of assessed risk factor(s) - Study design not relevant to this review protocol - Study does not contain a risk factor relevant to this review protocol
Vassiliadi, Dimitra Argyro, Dimopoulou, Ioanna, Tzanela, Marinella et al. (2014) Longitudinal assessment of adrenal function in the early and prolonged phases of critical illness in septic patients: relations to cytokine levels and outcome. The Journal of clinical endocrinology and metabolism 99(12): 4471-80	- Study does not contain a risk factor relevant to this review protocol
Voss, Martin, Batarfi, AbdulAziz, Steidl, Eike et al. (2019) Adrenal Insufficiency in Patients with Corticosteroid-Refractory Cerebral Radiation	- Study design not relevant to this review protocol *retrospective cohort study*

Study	Reason for exclusion
Necrosis Treated with Bevacizumab. Journal of clinical medicine 8(10)	
Wang, Peng-Fei, Chen, Yang, Song, Si-Ying et al. (2017) Immune-Related Adverse Events Associated with Anti-PD-1/PD-L1 Treatment for Malignancies: A Meta-Analysis. Frontiers in pharmacology 8: 730	- Study does not report adrenal insufficiency diagnosis or association data *Incidence only*
Wang, Wen-Bo, She, Fei, Xie, Li-Fang et al. (2016) Evaluation of Basal Serum Adrenocorticotropic Hormone and Cortisol Levels and Their Relationship with Nonalcoholic Fatty Liver Disease in Male Patients with Idiopathic Hypogonadotropic Hypogonadism. Chinese medical journal 129(10): 1147-53	- Reference standard or method of diagnosis does not match the review protocol
Wang, Xiao, Heinrich, Daniel A, Kunz, Sonja L et al. (2021) Characteristics of preoperative steroid profiles and glucose metabolism in patients with primary aldosteronism developing adrenal insufficiency after adrenalectomy. Scientific reports 11(1): 11181	- Study does not contain a risk factor relevant to this review protocol
Whelan, Gareth, Sim, Julius, Smith, Benjamin et al. (2022) Are Corticosteroid Injections Associated With Secondary Adrenal Insufficiency in Adults With Musculoskeletal Pain? A Systematic Review and Meta-analysis of Prospective Studies. Clinical orthopaedics and related research 480(6): 1061-1074	- Study does not report adrenal insufficiency diagnosis or association data
Winchester Behr, T, Sonnenblick, M, Nesher, G et al. (2012) Hyponatraemia in older people as a sign of adrenal insufficiency: a case-control study. Internal medicine journal 42(3): 306-10	- Study does not report adrenal insufficiency diagnosis or association data
Xu, Hang, Tan, Ping, Zheng, Xiaonan et al. (2019) Immune-related adverse events following administration of anti-cytotoxic T-lymphocyte-associated protein-4 drugs: a comprehensive systematic review and meta-analysis. Drug design, development, and therapy 13: 2215-2234	- Systematic review used as source of primary studies
Yang, Yaxian, Liu, Jingfang, Yang, Kaili et al. (2021) Endocrine Adverse Events Caused by Different Types and Different Doses of Immune Checkpoint Inhibitors in the Treatment of Solid Tumors: A Meta-Analysis and Systematic Review. Journal of clinical pharmacology 61(3): 282-297	- Systematic review used as source of primary studies
Yu, Sherry H, Drucker, Aaron M, Lebwohl, Mark et al. (2018) A systematic review of the safety and efficacy of systemic corticosteroids in atopic	- Systematic review used as source of primary studies

Study	Reason for exclusion
dermatitis. Journal of the American Academy of Dermatology 78(4): 733-740e11	
Yuan, Hang, Mao, Jiaxi, Liu, Cong et al. (2020) Risk of adverse events in advanced hepatocellular carcinoma with immune checkpoint therapy: A systematic review and meta-analysis. Clinics and research in hepatology and gastroenterology 44(6): 845-854	- Systematic review used as source of primary studies
Yuen, K.C.J.; Moraitis, A.; Nguyen, D. (2017) Evaluation of evidence of adrenal insufficiency in trials of normocortisolemic patients treated with mifepristone. Journal of the Endocrine Society 1(4): 237-246	- Reference standard or method of diagnosis does not match the review protocol
Zargar, A H, Laway, B A, Masoodi, S R et al. (2001) A critical evaluation of signs and symptoms in the diagnosis of Addison's diseases. The Journal of the Association of Physicians of India 49: 523-6	- Study design not relevant to this review protocol *retrospective*
Zhai, Yinghong, Ye, Xiaofei, Hu, Fangyuan et al. (2019) Endocrine toxicity of immune checkpoint inhibitors: a real-world study leveraging US Food and Drug Administration adverse events reporting system. Journal for immunotherapy of cancer 7(1): 286	- Study does not report adrenal insufficiency diagnosis or association data - Study design not relevant to this review protocol *retrospective*
Zhang, Yixi, Wang, Jingyuan, Hu, Taobo et al. (2022) Adverse Events of PD-1 or PD-L1 Inhibitors in Triple-Negative Breast Cancer: A Systematic Review and Meta-Analysis. Life (Basel, Switzerland) 12(12)	- Systematic review used as source of primary studies
Zhou, Q.; Patel, S.; Hamidi, V. (2019) Clinical features of immune checkpoint inhibitor-related adrenal insufficiency: A retrospective analysis. Journal for ImmunoTherapy of Cancer 7(supplement1)	- Conference abstract
Zollner, Ekkehard W, Lombard, Carl, Galal, Ushma et al. (2011) Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids: is the early-morning serum adrenocorticotropic hormone (ACTH) a useful screening test?. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 22(6): 614-20	- Study does not address this clinical question *Assessment of various diagnostic tests*
Zollner, Ekkehard Werner (2007) Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2)--the risk as determined by gold standard adrenal function tests: a systematic review. Pediatric	- Systematic review used as source of primary studies

Study	Reason for exclusion
allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 18(6): 469-74	
Zollner, Ekkehard Werner, Lombard, Carl J, Galal, Ushma et al. (2012) Hypothalamic-pituitary-adrenal axis suppression in asthmatic school children. Pediatrics 130(6): e1512-9	- Reference standard or method of diagnosis does not match the review protocol
Zueger, Thomas, Jordi, Marlen, Laimer, Markus et al. (2014) Utility of 30- and 60-minute cortisol samples after high-dose synthetic ACTH-1-24 injection in the diagnosis of adrenal insufficiency. Swiss medical weekly 144: w13987	- Study does not contain any signs or symptoms relevant to this review protocol

I.2 Health Economic studies

None.