National Institute for Health and Care Excellence

Draft

Head injury: assessment and early management (update)

[M] Evidence review for identification of hypopituitarism (who to investigate)

NICE guideline <number>

Evidence reviews underpinning recommendations x to y and research recommendations in the NICE guideline

September 2022

Draft for consultation

These evidence reviews were developed by the Guideline Development Group NGC

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1.1 Review question

Which patients should be investigated for hypopituitarism after head injury?

1.1.1 Introduction

Hypopituitarism is a clinical state due to absence of or reduction in hormones produced by the pituitary gland. The hormones produced by the anterior part of the pituitary are growth hormone, gonadotrophins (luteinizing hormone, follicle stimulating hormone or LH, FSH), Thyroid Stimulating Hormone (TSH), prolactin and adrenocorticotrophic hormone, ACTH) while the main hormone produced by the posterior part of the pituitary is arginine vasopressin (AVP); in hypopituitarism these hormones may be deficient in isolation or in combination. In infants and children, congenital hypopituitarism and septo-optic dysplasia are causes for early onset hypopituitarism. In older children and in adults, pituitary and hypothalamic tumours, traumatic brain injury and pituitary haemorrhage may cause hypopituitarism presenting in later life with varying severity.

Hypopituitarism may present acutely with cortisol deficiency and central diabetes insipidus, for instance with traumatic brain injury. Cortisol deficiency is characterized by tiredness, lethargy and inability to handle stress with potential escalation to adrenal crisis, a life-threatening state. Inability to produce AVP causing central diabetes insipidus may lead to dehydration and hypernatraemia, which may also be life threatening, if not treated promptly. For those with a more insidious onset, growth and puberty may be adversely affected in children and sexual dysfunction may occur in adults. A reduction in the production of TSH may lead to hypothyroidism with clinical features of tiredness, constipation and low mood in both children and adults.

Treatment of hypopituitarism is generally well accepted by patients and outcomes are satisfactory although monitoring and optimisation of therapy need to be undertaken through regular endocrine review in both children and adults. This review question looks at which patients should be investigated for hypopituitarism after a head injury.

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	Inclusion: Infants, children and adults with head injury • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups. Include all severities Strata: Severity of TBI based on GCS • Mild GCS 13-15

	• Moderate 9-12 • Severe GCS 3-8 Note: • All different diagnostic techniques to be included and to note when diagnosis made • Definition of hypopituitarism will vary in studies. Report as in the studies. Exclusion: Adults and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
Prognostic variables under consideration	Risk factors for hypopituitarism in adults and children/infants with head injury: • Gender • Severity of injury (based on GCS score – mild/moderate/severe) • Severity of anatomical injury on CT brain (this includes intracranial injury) • Severity of extracranial injury (definition in the studies) • Direct anatomical injury to pituitary (imaging finding) • History of non-accidental injury • Evidence of post-head injury acute endocrinopathy e.g. diabetes insipidus • Raised intracranial pressure (ICP) • Hypotension • Hypoxia • Pupillary abnormalities • Predisposing conditions such as hypothyroidism, Addison's disease Same risk factors apply to both adults and children
Confounding factors	Key confounders: • Severity of injury (based on GCS score) • Severity of anatomical injury on CT brain • Severity of extracranial injury Studies will only be included if all of the key confounders have been accounted for in a multivariate analysis.
Outcomes	Diagnosis of hypopituitarism: • Clinical or biochemical diagnosis of hypopituitarism • Post-mortem diagnosis of hypopituitarism Notes: • Include diagnosis of hypopituitarism as defined in the studies • To note at what time-point the diagnosis of hypopituitarism is made in each study where possible • Clinical or biochemical-based diagnoses may include the use of tests to assess function (for example, testing for growth hormone deficiency, thyroid function or cortisol). • Growth failure in children is a post-mortem diagnosis
Study design	Cohort studies (prospective and retrospective) Systematic reviews and meta-analyses of the above Exclusion: • Non-English language studies

- Conference abstracts
- Case-control studies
- Studies not adjusted for pre-specified key confounders in a multivariable analysis
- Studies using a univariate analysis or matched groups

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 Prognostic evidence

1.1.4.1 Included studies

Five cohort/observational studies were included in the review;[1-3, 5, 6] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Tables 3-16).

Two studies[3, 6] were specifically in adults and two studies[2, 5] did not have a minimum age to be included but had mean ages consistent with an adult population and were therefore included under adults. The remaining study[1] was specifically in children.

See also the study selection flow chart in Appendix A, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

Population

All included studies were similar in that they did not limit inclusion criteria based on GCS, meaning any GCS could be included. However, one study did limit the population further by only allowing those with a head AIS score of at least 3 to be included.

All studies were indirect relative to the review protocol as they did not provide results separately for different GCS severity groups, which were specified as strata (mild, moderate and severe) in the review protocol meaning separate results for these three groups would be ideal.

Risk factors

For most risk factors there was only data from one study for each specific variation or definition of the prognostic factor, though for moderate vs. mild and severe vs. mild GCS two adult studies reported data for hypopituitarism (with definitions varying slightly between studies). It was not possible to meta-analyse these studies as they did not adjust for the same confounders.

No relevant clinical studies investigating the effects of the following risk factors on the development of hypopituitarism were identified:

- Severity of extracranial injury
- Direct anatomical injury to pituitary (on imaging)
- History of non-accidental injury
- Evidence of post-head injury acute endocrinopathy (e.g. diabetes insipidus)
- Pupillary abnormalities

Outcome

Outcome definition and time-point varied across the studies. Two studies reported hypopituitarism at similar time-points (measured close to admission but with re-testing to confirm at 1-3 months) but with slightly different definitions of the deficiencies included under hypopituitarism, one study reported post-traumatic pituitary dysfunction at longer time-points of 1 and 5 years, one study reported the presence of diabetes insipidus at a short time-point with mean time from admission to ICU to onset of diabetes insipidus being 1.2 (1.7) days, and the study in children reported specifically secondary adrenal insufficiency at a short time-point of 2-3 days post-admission.

Most studies reported adjusted odds ratios (ORs) but one study in adults reported results as adjusted hazard ratios (HRs) instead.

Confounders

All studies conducted a multivariable analysis, but different variables were analysed in the studies; none of the included studies covered all three of the pre-specified key confounders in the review protocol (severity of injury based on GCS score, severity of anatomical injury on CT brain and severity of extracranial injury) but these were included given the lack of other available evidence and this was considered in the risk of bias rating.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

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1.1.5 Summary of studies included in the prognostic evidence

Table 2: Summary of studies included in the evidence review

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
Children						
Dupuis 2010[1] N=28 analysed Retrospective	Inclusion: admitted to **paediatric** intensive care unit of single hospital following TBI Exclusion: expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected	Logistic regression analysis. Multiple regression analysis described adjusted for initial severity measures (GCS, intracranial hypertension and PRISM scores).	• GCS score (continuous) • Presence vs. absence of preadmission hypotension [defined as systolic blood pressure lower than 70 mmHg + (2x age in years)] or hypoxia (defined as SaO2 <90%) • Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg)	MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).	Secondary adrenal insufficiency – assessed at 2-3 days post-admission If all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l)	Risk of bias: high Indirectness: • Population – not stratified by GCS injury severity as in the protocol
Adults						
Hadjizacharia 2008[2] N=425 (whole cohort) or N=	Inclusion: admitted to single surgical ICU unit with head AIS ≥3 (blunt or penetrating	Risk factors with P<0.2 from bivariate analysis entered into	• GCS ≤8 vs. GCS >8	MV analysis: age <15 years vs. 15-55 years; mechanism of injury (blunt vs.	Diabetes insipidus – time-point assessed at unclear (mean time	Risk of bias: high Indirectness:

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
397 (subgroup excluding those with non-head AIS >3) analysed Prospective	injuries) between June 2005 and May 2007. Exclusion: none reported Mixture of children and adults but mean age consistent with adult population (37 years)	stepwise logistic regression model.	• Head Abbreviated Injury Scale (AIS) >3 vs. = 3	penetrating); systolic blood pressure <90 vs. ≥90 mmHg; Injury Severity Score <16 vs. ≥16; GCS ≤8 vs. >8; head AIS >3 vs. ≤3; face AIS >3 vs. ≤3; oedema yes vs. no; head fracture yes vs. no; subarachnoid haemorrhage yes vs. no; subdural haemorrhage yes vs. no; vault head fracture yes vs. no; intraparenchymal haemorrhage yes vs. no; intraventricular haemorrhage yes vs. no; pneumocephaly yes vs. no; and shift yes vs. no.	from admission to ICU to onset of diabetes insipidus was 1.2 (1.7) days) Criteria for diabetes insipidus were urine output 300 mL/hour for more than 3 hours, hypernatremia, hyperosmolarity, and the use of Desmopressin Acetate. Duration of treatment with Desmopressin Acetate was 1.6 (1.3) days and 1.7 (1.3) days for those with isolated head injury.	• Population – not stratified by GCS injury severity as in the protocol; limits to those with head AIS score of at least 3; and adults and children combined but mean age consistent with adult population.
Klose 2007[3] N=104 for TBI severity and n=27 for intracranial pressure analysed Prospective/retrospective	Inclusion: patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time.	Logistic regression analyses conducted to analyse association between pituitary insufficiency and potential predictive factors	• Moderate (9-12) GCS vs. mild GCS (13-15) • Severe GCS (3-8) vs. mild GCS (13-15) • Intracranial pressure >15 mmHg for >23 h vs. normal intracranial pressure	MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI – *Is unclear if adjusted*	Hypopituitarism – measured close to admission but only confirmed by re-testing at 1-3 months Deficiency in hypothalamic-pituitary-adrenal axis, secondary	Risk of bias: high Indirectness: • Population – not stratified by GCS injury severity as in the protocol

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	Exclusion: doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge.			*for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results.*	hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency	
Yang 2016[5] N=31,389 – unclear if all analysed Retrospective	Inclusion: patients suffering TBI (ICD-9 codes 800-804, 850-854) between 1996 and 2009 Exclusion: endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data	Cox proportional hazards models used to compute HRs and 95% confidence intervals after adjustment for comorbidities and sociodemographic characteristics.	• Gender (unclear if male or female used as referent) • Presence vs. absence of diabetes mellitus • Injury severity based on ICD-9 code: ○ Mild ○ Intracranial haemorrhage ○ Skull bone fracture	MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture).	Post-traumatic pituitary dysfunction – 1 and 5 year follow-up time-points Enrolled study subjects followed up until death or end of 2009. Following ICD-9 code used to define presence of pituitary	Risk of bias: high Indirectness: • Population – not stratified by GCS injury severity as in the protocol; and adults and children combined but mean age consistent with adult population.

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	errors or missing data Mixture of children and adults but mean age consistent with adult population (~40 years)				dysfunction: 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during the study period.	
You 2019[6] N=193 Retrospective	Inclusion: TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation Exclusion: pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records.	Binary logistic regression analysis performed to determine independent risk factors for TBI-induced hypopituitarism.	• Presence vs. absence of intracranial hypertension • Moderate GCS (9-12) vs. mild GCS (13-15) • Severe GCS (3-8) vs. mild GCS (13-15)	MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS).	Hypopituitarism – median (IQR) interval between brain injury and evaluation was 7.5 (3-34) days (re-testing to confirm at 1-3 months) Adrenocorticotropic hormone deficiency, hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia	Risk of bias: high Indirectness: • Population – not stratified by GCS injury severity as in the protocol

Study	Population	Analysis	Prognostic variables	Confounders	Outcomes	Limitations
	Mixture of children and adults but mean age consistent with adult population (~40 years)					

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2 See Appendix D for full evidence tables.

1.1.6 Summary of the prognostic evidence

Adults – Gender

Table 3: Clinical evidence summary: Gender (unclear if male or female used as referent)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Gender (unclear if male or female used as referent and could not work out from other data in paper) for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)	31,389 (1) – unclear if all analysed **1 year** Yang 2016[5]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted HR: 0.16 (0.10 to 0.26)
Gender (unclear if male or female used as referent and could not work out from other data in paper) for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild,	31,389 (1) – unclear if all analysed **5 years** Yang 2016[5]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted HR: 0.11 (0.09 to 0.14)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
intracranial haemorrhage or skull bone fracture)			

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
(c) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately

Adults – GCS

Table 4: Clinical evidence summary: GCS ≤8 vs. GCS >8

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
GCS ≤8 vs. GCS >8 for predicting **diabetes insipidus** (criteria were urine output 300 mL/hour for more than 3 hours, hypernatremia, hyperosmolarity, and the use of Desmopressin Acetate) (admitted to surgical ICU unit with head AIS ≥3 including blunt or penetrating injuries; mean age 37 years; 41.7% mild injury, 15.8% with moderate injury and 42.4% with severe injury based on GCS – exclusion criteria not reported) MV analysis: age <15 years vs. 15-55 years; mechanism of injury (blunt vs. penetrating); systolic blood pressure <90 vs. ≥90 mmHg; Injury Severity Score <16 vs. ≥16; GCS ≤8 vs. >8; head AIS >3 vs. ≤3; face AIS >3 vs. ≤3; oedema yes vs. no; head fracture yes vs. no; subarachnoid haemorrhage yes vs. no; subdural haemorrhage yes vs. no; vault head fracture yes vs. no; intraparenchymal haemorrhage yes vs. no; intraventricular haemorrhage yes vs. no; pneumocephaly yes vs. no; and shift yes vs. no.	425 (1) and 397 (1) for *whole cohort* and *subgroup with non-head AIS >3 excluded*, respectively **Mean time from admission to ICU to onset of diabetes insipidus was 1.2 (1.7) days** Hadjizacharia 2008[2]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted OR: *Whole cohort:* 3.36 (1.57 to 7.18) *Subgroup with non-head AIS >3 excluded: 3.92 (1.73 to 8.86)*

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study participation, study attrition, outcome measurement, confounding (for whole cohort only, not subgroup excluding those with non-head AIS >3) and statistical analysis/selecting reporting domains
(c) Downgraded by 2 increments for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately. Also only includes those with a head AIS score >3 which may limit the population compared to those seen in practice.

Table 5: Clinical evidence summary: Moderate (GCS 9-12) vs. mild (GCS 13-15) severity

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Moderate (GCS 9-12) vs. mild (GCS 13-15) severity for predicting **hypopituitarism** (deficiency in hypothalamic-pituitary-adrenal axis, secondary hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency) (patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time; median age 56 years in those with outcome and 39 years in those without outcome; 13.0% vs. 48.0% mild GCS, 6.0% vs. 21.0% moderate GCS and 81.0% vs. 31.0% severe GCS – exclusion criteria were doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge) MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI – *unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results*	104 (1) **Measured close to admission but results confirmed by re-testing at 1-3 months** Klose 2007[3]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 1.40 (0.11 to 17.70)
Moderate (GCS 9-12) vs. mild (GCS 13-15) severity for predicting **hypopituitarism** (adrenocorticotropic hormone deficiency, hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia) (TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation; mean age ~55 years; 51% mild GCS, 25% moderate GCS and 24% severe GCS – exclusion criteria were pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant	193 (1) **Median interval between brain injury and evaluation was 7.5 (IQR 3-34) days but results confirmed by re-testing at 1-3 months** You 2019[6]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 0.47 (0.13 to 1.77)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records) MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS)			

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, outcome measurement and study confounding domains
(c) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(d) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Table 6: Clinical evidence summary: Severe (GCS 3-8) vs. mild (GCS 13-15) severity

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Severe (GCS 3-8) vs. mild (GCS 13-15) severity for predicting **hypopituitarism** (deficiency in hypothalamic-pituitary-adrenal axis, secondary hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency) (patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time; median age 56 years in those with outcome and 39 years in those without outcome; 13.0% vs. 48.0% mild GCS, 6.0% vs. 21.0% moderate GCS and 81.0% vs. 31.0% severe GCS – exclusion criteria were doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge) MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and	104 (1) **Measured close to admission but results confirmed by re-testing at 1-3 months** Klose 2007[3]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 6.40 (0.44 to 93.90)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
BMI – *unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results*			
Severe (GCS 3-8) vs. mild (GCS 13-15) severity for predicting **hypopituitarism** (adrenocorticotropic hormone deficiency, hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia) (TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation; mean age ~55 years; 51% mild GCS, 25% moderate GCS and 24% severe GCS – exclusion criteria were pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records) MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS)	193 (1) **Median interval between brain injury and evaluation was 7.5 (IQR 3-34) days but results confirmed by re-testing at 1-3 months** You 2019[6]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 0.84 (0.17 to 4.09)

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, outcome measurement and study confounding domains
(c) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(d) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Adults – severity based on CT

Table 7: Clinical evidence summary: Head Abbreviated Injury Scale (AIS) score >3 vs. = 3

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Head AIS >3 vs. = 3 for predicting **diabetes insipidus** (criteria were urine output 300 mL/hour for more than 3 hours, hypernatremia, hyperosmolarity, and the use of Desmopressin Acetate) (admitted to surgical ICU unit with head AIS ≥3 including blunt or penetrating injuries; mean age 37 years; 41.7% mild injury, 15.8% with moderate injury and	425 (1) and 397 (1) for *whole cohort* and *subgroup with non-head AIS >3 excluded*, respectively **Mean time from admission to ICU to onset of diabetes insipidus was 1.2 (1.7) days**	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted OR: *Whole cohort:* 2.60 (1.13 to 5.97) *Subgroup with non-head AIS >3 excluded:*

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
42.4% with severe injury based on GCS – exclusion criteria not reported) MV analysis: age <15 years vs. 15-55 years; mechanism of injury (blunt vs. penetrating); systolic blood pressure <90 vs. ≥90 mmHg; Injury Severity Score <16 vs. ≥16; GCS ≤8 vs. >8; head AIS >3 vs. ≤3; face AIS >3 vs. ≤3; oedema yes vs. no; head fracture yes vs. no; subarachnoid haemorrhage yes vs. no; subdural haemorrhage yes vs. no; vault head fracture yes vs. no; intraparenchymal haemorrhage yes vs. no; intraventricular haemorrhage yes vs. no; pneumocephaly yes vs. no; and shift yes vs. no.	Hadjizacharia 2008[2]		*2.87 (1.20 to 6.89)*

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, confounding (for whole cohort only, not subgroup excluding those with non-head AIS >3) and statistical analysis/selecting reporting domains
(c) Downgraded by 2 increments for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately. Also only includes those with a head AIS score >3 which may limit the population compared to those seen in practice

Adults – injury severity based on ICD-9 code

Table 8: Clinical evidence summary: Mild head injury vs. not mild based on ICD-9 code

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Mild head injury vs. not mild based on ICD-9 code for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild,	31,389 (1) – unclear if all analysed **1 year** Yang 2016[5]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted HR: 1.78 (0.96 to 3.28)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
intracranial haemorrhage or skull bone fracture)			
Mild head injury vs. not mild based on ICD-9 code for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)	31,389 (1) – unclear if all analysed **5 years** Yang 2016[5]	VERY LOW[a,b,d] Due to risk of bias, indirectness	Adjusted HR: 1.41 (1.07 to 1.87)

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
(c) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(d) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately

Table 9: Clinical evidence summary: Intracranial haemorrhage vs. not based on ICD-9 code

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Intracranial haemorrhage vs. not based on ICD-9 code for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data)	31,389 (1) – unclear if all analysed **1 year** Yang 2016[5]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted HR: 1.76 (1.01 to 3.08)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)			
Intracranial haemorrhage vs. not based on ICD-9 code for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)	31,389 (1) – unclear if all analysed **5 years** Yang 2016[5]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted HR: 1.46 (1.14 to 1.87)

(a) *Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias*
(b) *Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains*
(c) *Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately*

Table 10: Clinical evidence summary: Skull bone fracture vs. not based on ICD-9 code

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Skull bone fracture vs. not based on ICD-9 code for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01,	31,389 (1) – unclear if all analysed **1 year** Yang 2016[5]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted HR: 3.77 (1.94 to 7.32)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)			
Skull bone fracture vs. not based on ICD-9 code for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)	31,389 (1) – unclear if all analysed **5 years** Yang 2016[5]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted HR: 1.41 (0.90 to 2.21)

(a) *Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias*
(b) *Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains*
(c) *Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately*
(d) *Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)*

Adults – presence vs. absence of intracranial hypertension/abnormal intracranial pressure

Table 11: Clinical evidence summary: Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg) for predicting **hypopituitarism** (adrenocorticotropic hormone deficiency,	193 (1) **Median interval between brain injury**	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted OR: 3.21 (1.15 to 8.98)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia) (TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation; mean age ~55 years; 51% mild GCS, 25% moderate GCS and 24% severe GCS – exclusion criteria were pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records) MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS)	**and evaluation was 7.5 (IQR 3-34) days but results confirmed by re-testing at 1-3 months** You 2019[6]		

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, outcome measurement and study confounding domains
(c) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Table 12: Clinical evidence summary: Intracranial pressure >15 mmHg for at least 24 h vs. normal pressure

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Intracranial pressure >15 mmHg for at least 24 h vs. normal pressure for predicting **hypopituitarism** (deficiency in hypothalamic-pituitary-adrenal axis, secondary hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency) (patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time; median age 56 years in those with outcome and 39 years in those without outcome; 13.0% vs. 48.0% mild GCS, 6.0% vs. 21.0% moderate GCS and 81.0% vs. 31.0% severe GCS – exclusion criteria were doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous	27 (1) **Measured close to admission but results confirmed by re-testing at 1-3 months** Klose 2007[3]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 1.40 (0.11 to 17.70)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge) MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI – *unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results*			

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
(c) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(d) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Adults – presence vs. absence of predisposing conditions

Table 13: Clinical evidence summary: Diabetes mellitus vs. no diabetes mellitus

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Diabetes mellitus vs. no diabetes mellitus for predicting **post-traumatic pituitary dysfunction** (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)	31,389 (1) – unclear if all analysed **1 year** Yang 2016[5]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted HR: 2.41 (1.21 to 4.81)
Diabetes mellitus vs. no diabetes mellitus for predicting **post-traumatic pituitary**	31,389 (1) – unclear if all analysed	VERY LOW[a,b,c]	Adjusted HR: 2.12

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)	**5 years** Yang 2016[5]	Due to risk of bias, indirectness	(1.52 to 2.96)

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
(c) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately

Children – GCS

Table 14: Clinical evidence summary: GCS as a continuous variable (post-resuscitation GCS)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
GCS as a continuous variable (post-resuscitation GCS) for predicting **secondary adrenal insufficiency** (if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l) (admitted to ICU of single centre following TBI; median age 12 years in groups with and without the outcome; median GCS 7 vs. 9 in those with and without outcome, respectively – exclusion criteria were expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected)	28 (1) **Assessed at 2-3 days post-admission** Dupuis 2010[1]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 0.30 (0.08 to 1.11)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).			

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
(c) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(d) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Children – presence vs. absence of preadmission hypoxia or hypotension

Table 15: Clinical evidence summary: Presence vs. absence of preadmission hypoxia or hypotension

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Presence of preadmission hypoxia (defined as SaO2 <90%) or hypotension [defined as systolic blood pressure lower than 70 mmHg + (2x age in years)] for predicting **secondary adrenal insufficiency** (if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l) (admitted to ICU of single centre following TBI; median age 12 years in groups with and without the outcome; median GCS 7 vs. 9 in those with and without outcome, respectively – exclusion criteria were expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected) MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).	28 (1) **Assessed at 2-3 days post-admission** Dupuis 2010[1]	VERY LOW[a,b,c,d] Due to risk of bias, imprecision, indirectness	Adjusted OR: 0.61 (0.03 to 13.46)

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, outcome measurement and study confounding domains
(c) Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)
(d) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Children – presence vs absence of intracranial hypertension

Table 16: Clinical evidence summary: Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg)

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Presence of intracranial hypertension (intracranial pressure ≥20 mmHg) for predicting **secondary adrenal insufficiency** (if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l) (admitted to ICU of single centre following TBI; median age 12 years in groups with and without the outcome; median GCS 7 vs. 9 in those with and without outcome, respectively – exclusion criteria were expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected) MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).	28 (1) **Assessed at 2-3 days post-admission** Dupuis 2010[1]	VERY LOW[a,b,c] Due to risk of bias, indirectness	Adjusted OR: 298.87 (1.22 to 73134.17)

(a) Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
(b) Risk of bias was identified for study attrition, outcome measurement and study confounding domains
(c) Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

See Appendix F for full GRADE tables.

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 G.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

No original economic modelling was undertaken.

1.1.11 Evidence statements

Economic

- No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1. The outcomes that matter most

Diagnosis

Diagnosis of hypopituitarism in infants, children and adults with head injury by prognostic risk factors (gender, severity of injury, severity of anatomical injury on CT brain, severity of extracranial injury, direct anatomical injury to pituitary, history of non-accidental injury, evidence of post-head injury acute endocrinopathy, raised intracranial pressure, hypotension, hypoxia, pupillary abnormalities and predisposing conditions such as hypothyroidism or Addison's disease) was the relevant outcome for this review. Diagnosis could be clinical or biochemical or post-mortem diagnosis of hypopituitarism, and the time-point was noted. Adjusted odds ratios were the measures most used in assessing whether a risk factor diagnosed hypopituitarism, but one study used adjusted hazard ratios. Outcome definition and time-points varied across the studies.

1.1.12.2 The quality of the evidence

Evidence was limited in quantity, with 5 cohort studies in total, 2 in an adult population, 2 in a mixed adult and children population (but were considered as adults as the mean age was 37 years) and 1 study in children only.

The limitations associated with the evidence discussed under various headings below, as well as current practice, were taken into account when considering any recommendations that could be made in this area. The contribution of these limitations to decisions that were made are discussed under the benefits and harms section.

Population

The results were indirect as there was no separation by GCS severity group (mild moderate and severe) as specified as strata in the review protocol. One study also may have limited the population, as they only included those with head AIS score>3. There was a lot of heterogeneity of trauma types and mechanisms of injury.

Risk factors

There was a lack of evidence for each risk factor. There was mostly one study per risk factor and several which had no relevant studies.

Grouping and meta-analysis

The studies could not be meta-analysed as there was mostly one study for each specific variation or definition of the prognostic factor and where there were two, they did not adjust for the same confounders.

Confounders

Although some were, not all pre-specified confounders (severity of injury based on GCS score, severity of anatomical injury on CT brain and severity of extracranial injury) were included in the multivariate analyses within the studies. The protocol required all to have been accounted for in multivariate analyses in order to be included in the review, however because no studies did this the studies were included and downgraded.

Risk of bias

There was a very low quality of evidence rating throughout the review, mainly due to study attrition, prognostic factor measurement, outcome measurement and study confounding domains. There were few studies and they were in diverse circumstances or mechanisms of injury and included different ages within the studies.

Imprecision

Imprecision occurred where the line of no effect (one) was crossed, which occurred in some of the evidence (stratified below as statistically significant or not).

1.1.12.3 Benefits and harms

Statistically significant risk factors:

Adults:

The evidence suggested that gender was predictive of post-traumatic pituitary dysfunction (defined by ICD-9 code) at 1 and 5 years, but the referent group was not reported so the direction of risk was not clear.

GCS≤8 was predictive of diabetes insipidus when compared to GCS>8 for a population who were admitted to surgical ICU with head AIS ≥3 including blunt or penetrating injuries. This was predictive for both the whole cohort and the non-head AIS >3 excluded sub-group. Head AIS >3 was predictive of diabetes insipidus compared to Head AIS = 3 in the same setting.

Mild head injury, intracranial haemorrhage, skull bone fracture and diabetes were predictive of post-traumatic pituitary dysfunction compared to not having these at 1 and 5 years based on ICD-9 code. The evidence came mainly from one study and the committee discussed that injury severity based on ICD-9 code was typically used for administrative purposes and not for distinguishing severity.

Children:

The presence of intracranial hypertension was predictive of secondary adrenal insufficiency in children. However, the committee thought this was not that useful in clinical terms, except raised idiopathic intracranial hypertension implies severe injury.

Statistically non-significant risk factors:

Adults:

Severity (GCS) for predicting hypopituitarism varied, in one study Moderate (GCS 9-12) was predictive compared to mild severity (GCS 13-15), while in another mild (GCS 13-15) was predictive over moderate severity (GCS 9-12). In the same studies Severe (GCS 3-8) was predictive compared to mild (GCS 13-15) for predicting hypopituitarism in one study, but Mild (GCS 13-15) was predictive compared to severe (GCS 3-8) in another.

Children:

Intracranial pressure >15mmHg compared to normal; GCS as a continuous variable and presence of preadmission hypoxia or hypotension were not predictive.

Overall, the evidence was limited so the committee supplemented this with their expertise to inform the recommendations. They discussed that it is not fully understood why head injury causes hypopituitarism, and there could be various reasons. Higher severity of head injury is more likely to cause higher risk of hypopituitarism, however any severity of head injury could cause pituitary dysfunction. Current practice for screening for hypopituitarism is variable but it is most commonly identified on CT in the emergency department but this may not identify pituitary, stalk or hypothalamus. It can also depend on the Clinician's familiarity with hypopituitarism as to whether it is diagnosed. Testing in the emergency department may not be useful because the acute phase will stimulate cortisol so it would be difficult to tell if there was hypoadrenalism. It is also difficult to assess for central hypothyroidism or central hypogonadism in the acute phase, as these are often low in the context of intercurrent illness. Therefore, the committee thought that it would be better to investigate it in those who were admitted to hospital with head injury with clinical symptoms such as hypotension or hyponatraemia. Where imaging of the head has taken place and or patients have been hospitalised the committee suggested this would provide an opportunity for referral to a specialist.

Hypopituitarism could be identified immediately in the weeks or months following a head injury or by delayed symptoms. Posterior hypopituitarism, which would present itself with diabetes insipidus (thirst polyuria polydipsia, hypernatraemia) occurs early following head injury and may resolve itself spontaneously. The committee highlighted that identification of hypopituitarism may not be straightforward as there are many non-specific symptoms, making it difficult to suggest definitive symptoms for hypopituitarism. Some symptoms that may be indicative of hypopituitarism in adults include one or more of the following: stomach pain, decreased appetite, nausea and vomiting, constipation; excessive thirst and urination; fatigue and/or weakness; anaemia (not having enough red blood cells (this would take at least three months to manifest)); headache and dizziness; sensitivity to cold; weight loss or weight gain; muscles aches. In women it could include: loss of armpit or pubic hair, decreased sex drive, infertility, problems with breast feeding, no menstrual or irregular periods. In men: loss of hair (on the face, or in the armpits or pubic area), decreased sex drive, infertility, erectile dysfunction. The committee agreed that these were too general to include in the recommendation but that lower or higher sodium and low blood pressure are assessed at hospital admission and persistence of these may indicate the need for further investigation. Further investigation in endocrinology may need to be conducted where people have symptoms that persist such as depression or lethargy or are not progressing at the expected recovery rate.

In children immediate hypopituitarism may manifest as polyuria, dehydration, polydipsia and tiredness or fatigue. Delayed symptoms may include slow growth, tiredness and late puberty. The committee emphasised that if hypopituitarism is suspected it is important to urgently refer the child to a paediatric endocrinologist.

The committee noted that posterior hypopituitarism can occur early on following head injury but this may resolve spontaneously.

1.1.12.4 Cost effectiveness and resource use

No economic evaluations were found for this question.

Hypopituitarism can cause under-development of children and poor quality of life for adults and children. A number of tests are used to diagnose hypopituitarism, since it affects the

production of several different hormones. These include thyroid function, morning cortisol, prolactin, insulin-like growth factor 1, as well as review of growth in children. The main treatment is by hormone replacement, such as human growth hormone (see NICE technology appraisals TA64 and TA188), thyroid hormone (see NICE guideline NG145), desmopressin, hydrocortisone, testosterone/oestrogen.

Given the lack of clinical and economic evidence, the committee did not recommend widespread testing for hypopituitarism. However, they did highlight some symptoms during the hospital admission that might require further investigation: low blood pressure and low sodium (or high sodium in the case of diabetes insipidus). These would be routinely assessed during a hospital admission.

The committee also, recommended that the symptoms of hypopituitarism be included in discharge information, so that patients are empowered to seek appropriate help if symptoms emerge or persist after discharge. So, there might be an increase in testing for hypopituitarism. It is also intended that people will get referred for appropriate specialist care sooner, perhaps with an endocrinologist. The size of this resource impact is uncertain, but it is expected that there will be a reduction in investigations for alternative conditions.

1.1.12.5 Other factors the committee took into account

None.

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Appendices

Appendix A – Review protocols

Review protocol for identification of hypopituitarism (who to investigate)

ID	Field	Content
0.	PROSPERO registration number	[Complete this section with the PROSPERO registration number once allocated]
1.	Review title	Identification of hypopituitarism after head injury <u>Hypopituitarism</u> Inadequate secretion of one or more of the hormones secreted by the pituitary is known as hypopituitarism. TBI may cause pituitary gland dysfunction contributing to significant morbidity and mortality from TBI. Hormones secreted by pituitary gland: ACTH (adrenocorticotropic hormone): deficiency causes weakness, lethargy, weight loss. Findings: hypotension, hyponatremia, hypoglycaemia, hypercalcaemia, anaemia, fatigue Growth hormone: deficiency causes decreased energy, low mood, neuropsychiatric and cognitive symptoms. Finding: decreased lean body mass, increased fat mass, altered metabolic profile, decreased exercise capacity, LH **Luteinizing Hormone** /FSH Follicle stimulating hormone: deficiency in women, symptoms include irregular or stopped menstrual periods and infertility. In men, symptoms include loss of body and facial hair, weakness, lack of interest in sexual activity, erectile dysfunction, and infertility.

		TSH thyroid stimulating hormone (TSH) deficiency presents with fatigue, lethargy, cold intolerance, and weight gain. Vasopressin: deficiency causes polyuria, polydipsia, nocturia, incontinence
2.	Review question	Which patients should be investigated for hypopituitarism after head injury?
3.	Objective	To identify which patients should be investigated for hypopituitarism after head injury. There is currently no guidance for the screening and detection of hypopituitarism patients with TBI, with significant variation in practice.
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 Other searches: • Inclusion lists of systematic reviews

		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	Hypopituitarism after head injury
6.	Population	i) Inclusion: Infants, children and adults with people with head injury • Adults (aged ≥16 years) • Children (aged ≥1 to <16 years) • Infants (aged <1 year) Mixed population studies will be included but downgraded for indirectness. Cut-off of 60% will be used for all age groups. Include all severities Strata: Severity of TBI based on GCS • Mild GCS 13-15 • Moderate 9-12 • Severe GCS 3-8 Note:

		Include all different diagnostic techniques and note when the diagnosis was made. Definition of hypopituitarism will vary in studies. Report as in the studies. Exclusion: Adults and children (including infants under 1 year) with superficial injuries to the eye or face without suspected or confirmed head or brain injury.
7.	Eligibility criteria – risk factors	Risk factors for hypopituitarism in adults and children/infants with head injury: • Gender • Severity of injury (based on GCS score – mild/moderate/severe) • Severity of anatomical injury on CT brain (this includes intracranial injury) • Severity of extracranial injury (definition in the studies) • direct anatomical injury to pituitary (imaging finding) • history of non-accidental injury • evidence of post-head injury acute endocrinopathy e.g., diabetes insipidus • Raised intracranial pressure (ICP) • hypotension • hypoxia • Pupillary abnormalities • Predisposing conditions such as hypothyroidism, Addison's disease Same risk factors apply to both adults and children

8.	Eligibility criteria – comparator(s) / control or reference (gold) standard	Absence of risk factors
9.	Types of study to be included	Cohort studies (prospective and retrospective) Systematic reviews and meta-analyses of the above Case-control studies will be excluded. Key confounders: • Severity of injury (based on GCS score) • Severity of anatomical injury on CT brain • Severity of extracranial injury Studies will only be included if all of the key confounders have been accounted for in a multivariate analysis.
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available. Studies not adjusted for pre-specified key confounders in a multivariable analysis. Studies using a univariate analysis or matched groups.
11.	Context	TBI may cause pituitary gland dysfunction contributing to significant morbidity and mortality from TBI. There is currently no guidance for the screening and detection of hypopituitarism patients with TBI, with significant variation in practice.
12.	Primary outcomes (critical outcomes)	Diagnosis of hypopituitarism: • Clinical or biochemical diagnosis of hypopituitarism • Post-mortem diagnosis of hypopituitarism Notes:

		Include diagnosis of hypopituitarism as defined in the studies To note at what time-point the diagnosis of hypopituitarism is made in each study where possible Clinical or biochemical-based diagnoses may include the use of tests to assess function (for example, testing for growth hormone deficiency, thyroid function or cortisol). Growth failure in children is a post-mortem diagnosis GC comment: Do not specify tests for diagnosis of hypopituitarism. Note type of diagnostic test for hypopituitarism used in the studies. Diagnostic testing for hypopituitarism: Basal Pituitary investigations are typically similar at the time of presentation and 1 year later. These are generally: electrolytes, cortisol + ACTH, IGF-I, Prolactin, thyroid function. Depending on the circumstances, some centres might want to do a synacthen instead of random cortisol + ACTH. In children, there is a case to investigate growth failure. For this, a dynamic function test may be required at the 1 year mark.
13.	Data extraction (selection and coding)	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.	
14.	Risk of bias (quality) assessment	The methodological quality of each study will be assessed using the QUIPS checklist. The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
15.	Strategy for data synthesis	• meta-analyses will be performed if possible using Cochrane Review Manager (RevMan5) depending on the appropriateness of data. • Studies will be pooled if they are relatively homogenous and have adjusted for the same confounders. • 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. For more information please see the separate Methods report for this guideline.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: None identified	
17.	Type and method of review	☐	Intervention
		☒	Diagnostic association

		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	[For the purposes of PROSPERO, the date of commencement for the systematic review can be defined as any point after completion of a protocol but before formal screening of the identified studies against the eligibility criteria begins. A protocol can be deemed complete after sign-off by the NICE team with responsibility for quality assurance.]	
21.	Anticipated completion date	[Give the date by which the guideline is expected to be published. This field may be edited at any time. All edits will appear in the record audit trail. A brief explanation of the reason for changes should be given in the Revision Notes facility.]	
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 National Guideline Centre 5b Named contact e-mail [Guideline email]@nice.org.uk [Developer to check with Guideline Coordinator for email address] 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and [National Guideline Alliance / National Guideline Centre / NICE Guideline Updates Team / NICE Public Health Guideline Development Team] [Note it is essential to use the template text here and one of the centre options to enable PROSPERO to recognise this as a NICE protocol]		
24.	Review team members	[Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.] From the National Guideline Centre: [Guideline lead] [Senior systematic reviewer] Systematic reviewer [Health economist]		

		[Information specialist] [Others]
25.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from 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: [NICE guideline webpage].
28.	Other registration details	[Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.]
29.	Reference/URL for published protocol	[Give the citation and link for the published protocol, if there is one.]
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. [Add in any additional agree dissemination plans.]	
31.	Keywords	Hypopituitarism, head injury	
32.	Details of existing review of same topic by same authors	NA	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	[Provide any other information the review team feel is relevant to the registration of the review.]	
35.	Details of final publication	www.nice.org.uk	

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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. The search covered all years
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later that were included in the previous guidelines will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. 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).[4] **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 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 (including any such studies included in the previous guidelines) will 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.

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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.[4]

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 Head Injury population and terms for Hypopituitarism. No filters were applied to cover both the intervention and diagnostic elements of the review.

Table 17: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 22 June 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 22 June 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Reviews to 2022 Issue 6 of 12 CENTRAL to 2022 Issue 6 of 12	
Epistemonikos (The Epistemonikos Foundation)	Inception to 22 June 2022	Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/

13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	Hypopituitarism/
27.	(Hypopituitarism* or hypopitiutaryism* or PTHP).ti,ab.
28.	(pituitary adj2 (insufficien* or dysfunction* or injur* or damage* or function* or fail* or deficien* or hypofunction*)).ti,ab.
29.	(hypophysis adj2 (insufficien* or dysfunction* or injur* or damage* or function* or fail* or deficien* or hypofunction*)).ti,ab.
30.	Simmond* disease.ti,ab.
31.	or/26-30
32.	25 and 31

11 Embase (Ovid) search terms

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or cranial or cerebral or skull) adj4 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/

22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	hypopituitarism/
28.	(Hypopituitarism* or hypopitiutaryism* or PTHP).ti,ab.
29.	(pituitary adj2 (insufficien* or dysfunction* or injur* or damage* or function* or fail* or deficien* or hypofunction*)).ti,ab.
30.	(hypophysis adj2 (insufficien* or dysfunction* or injur* or damage* or function* or fail* or deficien* or hypofunction*)).ti,ab.
31.	Simmond* disease.ti,ab.
32.	or/27-30
33.	26 and 32

12 Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Craniocerebral Trauma] this term only
#2.	MeSH descriptor: [Brain Injuries] explode all trees
#3.	MeSH descriptor: [Coma, Post-Head Injury] this term only
#4.	MeSH descriptor: [Head Injuries, Closed] explode all trees
#5.	MeSH descriptor: [Head Injuries, Penetrating] this term only
#6.	MeSH descriptor: [Intracranial Hemorrhage, Traumatic] explode all trees
#7.	MeSH descriptor: [Skull Fractures] explode all trees
#8.	((skull or cranial) near/3 fracture*):ti,ab
#9.	((head or brain or craniocerebral or intracranial or cranial or skull) near/3 (injur* or trauma*)):ti,ab
#10.	(trauma* and ((subdural or intracranial) near/2 (h?ematoma* or h?emorrhage* or bleed*))):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12.	MeSH descriptor: [Hypopituitarism] this term only
#13.	(Hypopituitarism* or hypopitiutaryism* or PTHP):ti,ab
#14.	(pituitary near/2 (insufficien* or dysfunction* or injur* or damage* or function* or fail*)):ti,ab
#15.	Simmond* disease:ti,ab
#16.	#12 or #13 or #14 or #15
#17.	#11 and #16

13 Epistemonikos search terms

1.	(title:((Hypopituitarism* OR hypopitiutaryism* OR PTHP)) OR abstract:((Hypopituitarism* OR hypopitiutaryism* OR PTHP))) OR (title:((pituitary AND (insufficien* OR dysfunction* OR injur* OR damage* OR function* OR fail* OR deficien* OR hypofunction*))) OR abstract:((pituitary AND (insufficien* OR dysfunction* OR injur* OR damage* OR function* OR fail* OR deficien* OR hypofunction*)))) OR (title:((hypophysis AND (insufficien* OR dysfunction* OR injur* OR damage* OR function* OR fail* OR deficien* OR hypofunction*))) OR abstract:((hypophysis AND (insufficien* OR dysfunction* OR injur* OR damage* OR function* OR fail* OR deficien* OR hypofunction*)))) OR (title:(Simmond* disease) OR abstract:(Simmond* disease))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Head Injury 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 for health economics, and all years for quality-of-life studies.

Table 18: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
	Quality of Life 1946 – 22 June 2022	
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 22 June 2022	
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 – 22 June 2022	English language

Medline (Ovid) search terms

1.	craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or exp head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/
2.	((skull or cranial) adj3 fracture*).ti,ab.
3.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
4.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.

5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to English language
26.	economics/
27.	value of life/
28.	exp "costs and cost analysis"/
29.	exp Economics, Hospital/
30.	exp Economics, medical/
31.	Economics, nursing/
32.	economics, pharmaceutical/
33.	exp "Fees and Charges"/
34.	exp budgets/
35.	budget*.ti,ab.
36.	cost*.ti.
37.	(economic* or pharmaco?economic*).ti.
38.	(price* or pricing*).ti,ab.
39.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
40.	(financ* or fee or fees).ti,ab.
41.	(value adj2 (money or monetary)).ti,ab.
42.	or/26-41
43.	quality-adjusted life years/
44.	sickness impact profile/

45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/43-61
63.	25 and (42 or 62)

24 **Embase (Ovid) search terms**

1.	head injury/
2.	exp brain injury/
3.	skull injury/ or exp skull fracture/
4.	((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)).ti,ab.
5.	((skull or cranial) adj3 fracture*).ti,ab.
6.	(trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))).ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	(conference abstract or conference paper).pt.
12.	case report/ or case study/
13.	(letter or comment*).ti.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/

21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	health economics/
28.	exp economic evaluation/
29.	exp health care cost/
30.	exp fee/
31.	budget/
32.	funding/
33.	budget*.ti,ab.
34.	cost*.ti.
35.	(economic* or pharmaco?economic*).ti.
36.	(price* or pricing*).ti,ab.
37.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
38.	(financ* or fee or fees).ti,ab.
39.	(value adj2 (money or monetary)).ti,ab.
40.	or/27-39
41.	quality-adjusted life years/
42.	"quality of life index"/
43.	short form 12/ or short form 20/ or short form 36/ or short form 8/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/41-61

63.	26 and (40 or 62)

25 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE ALL TREES
#7.	MeSH DESCRIPTOR Skull Fractures EXPLODE ALL TREES
#8.	(((skull or cranial) adj3 fracture*))
#9.	(((head or brain or craniocerebral or intracranial or cranial or skull) adj3 (injur* or trauma*)))
#10.	((trauma* and ((subdural or intracranial or brain) adj2 (h?ematoma* or h?emorrhage* or bleed*))))
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

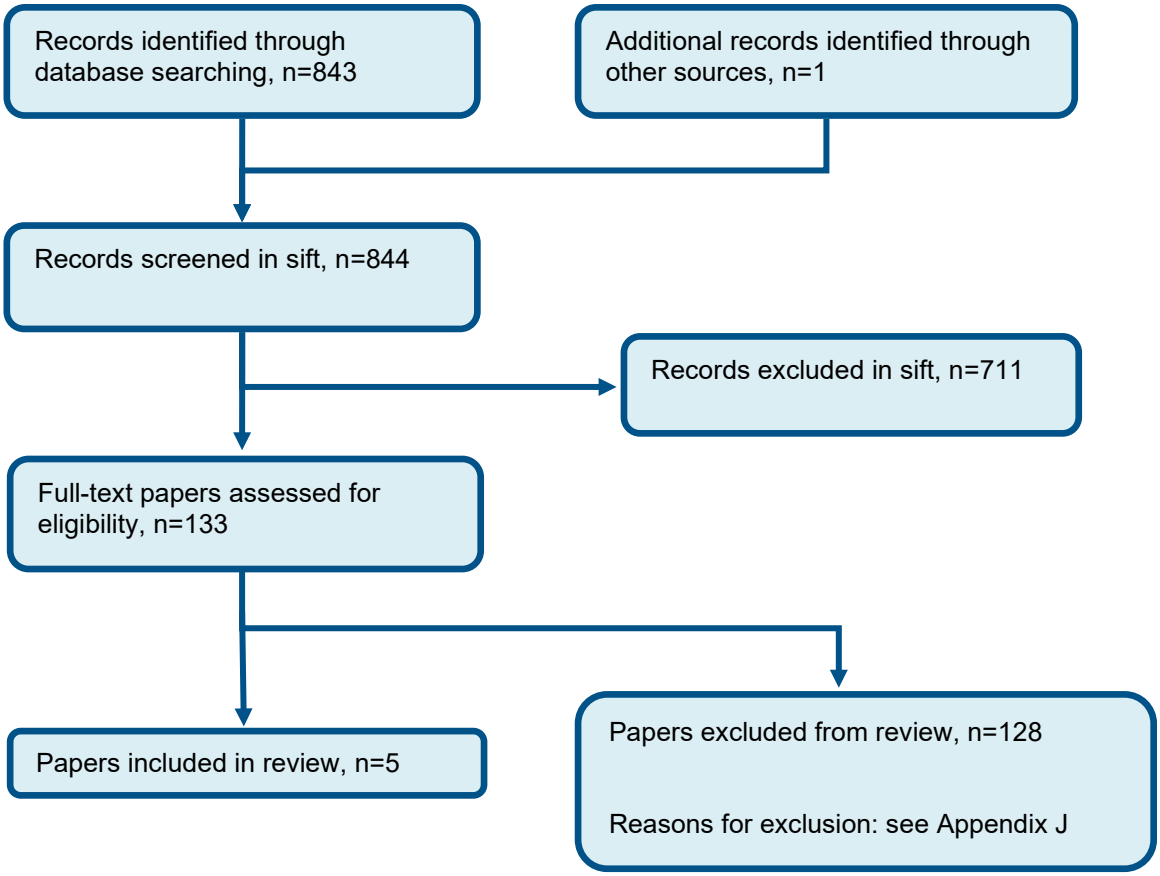
26 **INAHTA search terms**

1.	((((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*)))):[Title]) AND (((trauma* and ((subdural or intracranial or brain) and (haematoma* or hematoma* or haemorrhage* or hemorrhage* or bleed*)))):[Title])) OR ((((skull or cranial) and fracture*)):[Title] OR (((skull or cranial) and fracture*)):[abs]) OR ((((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*))):[Title] OR (((head or brain or craniocerebral or intracranial or cranial or skull) and (injur* or trauma*))):[abs]) OR ("Skull Fractures"[mhe]) OR ("Intracranial Hemorrhage, Traumatic"[mhe]) OR ("Head Injuries, Penetrating"[mh]) OR ("Head Injuries, Closed"[mhe]) OR ("Coma, Post-Head Injury"[mh]) OR ("Brain Injuries"[mhe]) OR ("Craniocerebral Trauma"[mh])

27

Appendix C –Prognostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of identification of hypopituitarism (who to investigate)



Appendix D – Prognostic evidence

Reference	Dupuis 2010[1]
Study type and analysis	Retrospective study Logistic regression analysis conducted using adrenal insufficiency as dependent variable and potential explanatory variables (PRISM an GCS scores, etomidate use, intracranial hypertension, preadmission hypotension or hypoxia and CT findings). Multiple regression analysis described adjusted for initial severity measures (GCS, intracranial hypertension and PRISM scores). Significance indicated by P<0.05.
Number of participants and characteristics	N= 31 eligible (n=28 with data that could be analysed) • GCS score (continuous), n=28 • Preadmission hypotension or hypoxia, n=9 • No preadmission hypotension or hypoxia, n=19 • Intracranial hypertension, n=17 • No intracranial hypertension, n=11 **Inclusion criteria:** admitted to paediatric intensive care unit of single hospital following TBI. **Exclusion criteria:** expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected. **Population characteristics:** given separately for n=10 with and n=18 without secondary adrenal insufficiency (continuous values are median (IQR) • Age: 12 (10-12) vs. 12 (10-14) years • Male sex, 70% vs. 83% • GCS: 7 (6-7) vs. 9 (6-11) • PRISM score: 19 (12-24) vs. 14 (11-17) • Paediatric Trauma score: 5 (4-5) vs. 5 (4-8) • Received etomidate, 80% vs. 67%

Reference	Dupuis 2010[1]
	• Preadmission hypotension or hypoxia, 50% vs. 28% • Intracranial hypertension, 90% vs. 44% • CT findings: ○ Cerebral oedema, 70% vs. 56% ○ Subarachnoid haemorrhage, 50% vs. 22% ○ Subdural or epidural haematoma, 30% vs. 33% ○ Intracerebral haematoma, 60% vs. 67% ▪ Frontal-temporal lobes, 60% vs. 44% ▪ Other location, 40% vs. 33% • Markers of clinical instability at time of endocrine evaluation and endocrine data: ○ PELOD: 12 (3-12) vs. 3 (2-11) ○ Mechanical ventilation duration: 11 (8-21) vs. 5 (1-9) days ○ Daily mean cortisol: 74 (63-80) vs. 318 (207-403) nmol/l ○ Daily maximal cortisol: 150 (120-185) vs. 613 (488-677) nmol/l ○ Daily mean ACTH: 1.8 (1.5-2.2) vs. 3.0 (2.1-5.1) pmol/l ○ Free urinary cortisol: 31 (20-90) vs. 293 (254-432) nmol/m^2 24 h **Population source:** retrospective review of those admitted between May 2006 and May 2009 to Paediatric Intensive Care Unit of single hospital (Grenoble University Hospital) following TBI. Eligible patients identified from archives of the intensive care unit and charts of eligible patients reviewed retrospectively.
Prognostic variables	Initial post-resuscitation GCS score (continuous variable) Presence of preadmission hypoxia or hypotension Absence of preadmission hypoxia or hypotension (referent) Presence of intracranial hypertension Absence of intracranial hypertension (referent) GCS interpreted as mild injury if GCS >13, moderate if between 9 and 13 and severe if <9. Intracranial hypertension defined as pressure >20 mmHg for at least 15 min. Pre-admission episodes of arterial hypotension [defined as systolic blood pressure lower than

Reference	Dupuis 2010[1]
	70 mmHg + (2x age in years)] and of hypoxia (defined as SaO2 <90%) were recorded.
Confounders	Assume full list of those included provided in table 2 as includes even those with lower P-values: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes). Has adjusted for key confounder of GCS score in protocol, but not: severity of anatomical injury on brain CT or severity of extracranial injury. Included given limited other evidence available.
Outcomes and effect sizes	Note that data is reported as log OR (95% confidence intervals) in the paper, which is extracted below. **<u>Secondary adrenal insufficiency at ~2-3 days post-admission</u>** **LogOR -1.2 (95% CI -2.6 to 0.1), P=0.07 for GCS (continuous)** **LogOR -0.5 (95% CI -3.6 to 2.6), P-0.75 for preadmission vs. no preadmission hypotension or hypoxia** **LogOR 5.7 (95% CI 0.2 to 11.2), P=0.03 for intracranial hypertension vs. no intracranial hypertension** Secondary adrenal insufficiency was defined as: if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l. Serial serum cortisol and plasms ACTH levels measured during a 24-h period. First at 8 am on second morning following admission with subsequent samples every 3 h for serum cortisol (total 9 samples) and every 6 h for ACTH (total 5 samples), ending after the third morning 8 am measurement. Patients in supine position during the study. All urine output collected during same 24 h period for evaluation of free urinary cortisol. Plasma cortisol measured using automated chemiluminescence assay. Plasma ACTH measured using radioimmunoassay. Urinary free cortisol measured using radioimmunoassay.
Comments	**Risk of bias (differences between risk factors indicated):** 1. Study participation — LOW 2. Study attrition — MODERATE 3. Prognostic factor measurement — MODERATE (for GCS as risk factor) or LOW (for other two risk factors) 4. Outcome Measurement — MODERATE 5. Study confounding — MODERATE 6. Statistical analysis — LOW

Reference	Dupuis 2010[1]
	OVERALL RISK OF BIAS HIGH **Indirectness (applies to all risk factors):** • Population – not stratified by severity of TBI based on GCS as in the review protocol and mild-severe included as a single group for analysis

Reference	Hadjizacharia 2008[2]
Study type and analysis	Prospective study Bivariate analysis performed to compare demographic and clinical characteristics between those with and without diabetes insipidus. Risk factors with P<0.2 from bivariate analysis entered into stepwise logistic regression model. Adjusted odds ratio and 95% CI derived for each risk factor in the model. Adjusted P<0.05 considered statistically significant.
Number of participants and characteristics	N=436 (n=425 analysed for adjusted odds ratios; subgroup with chest, abdomen and extremity AIS excluded, n=397) *Note that numbers given below for each risk factor group are for n=436 as not given for the n=425 analysed* • GCS ≤8, n=182 • GCS >8, n=254 • Head Abbreviated Injury Scale (AIS) >3, n=227 • Head AIS = 3, n=209 **Inclusion criteria:** admitted to single surgical ICU unit with head AIS ≥3 (blunt or penetrating injuries) between June 2005 and May 2007. **Exclusion criteria:** none reported **Population characteristics:** given for n=436 matching inclusion criteria, not separately for n=425 analysed (continuous values are mean (SD)) • Age: 37 (20) years • Male sex, 77.8%

Reference	Hadjizacharia 2008[2]
	• GCS: ○ ≤8, 42.4% ○ 9-12, 15.8% ○ >12, 41.7% • Intubation: ○ No endotracheal tube, 37.6% ○ Pre-hospital endotracheal tube, 5.1% ○ Endotracheal tube, 57.3% • Systolic blood pressure <90 mmHg, 3.8% • Blunt injury, 90% • Penetrating injury, 10% • Pathology: ○ Extradura haematoma, 11.2% ○ Subdural haemorrhage, 35.3% ○ Subarachnoid haemorrhage, 45.6% ○ Intraparenchymal haemorrhage, 32.1% ○ Intraventricular haemorrhage, 11.7% ○ Oedema, 16.3% ○ Diffuse axonal injury, 7.6% ○ Pneuomocephalus, 20.2% • Head AIS: ○ 3, 47.9% ○ 4, 20.6% ○ 5, 30.5% ○ 6, 0.9%

Reference	Hadjizacharia 2008[2]
	Population source: described as prospective study. Included all of those admitted to single surgical ICU (LAC+USC Medical Center surgical ICU) between June 2005 and May 2007.
Prognostic variables	GCS ≤8 GCS >8 (referent) Head AIS >3 Head AIS = 3 (referent) GCS reported to be that measured on admission. No further details for head AIS but assume at time of admission.
Confounders	Risk factors included in the model were as follows, though only independent predictor results given in table 6: age <15 years vs. 15-55 years; mechanism of injury (blunt vs. penetrating); systolic blood pressure <90 vs. ≥90 mmHg; Injury Severity Score <16 vs. ≥16; GCS ≤8 vs. >8; head AIS >3 vs. ≤3; face AIS >3 vs. ≤3; oedema yes vs. no; head fracture yes vs. no; subarachnoid haemorrhage yes vs. no; subdural haemorrhage yes vs. no; vault head fracture yes vs. no; intraparenchymal haemorrhage yes vs. no; intraventricular haemorrhage yes vs. no; pneumocephaly yes vs. no; and shift yes vs. no. Has adjusted for key confounder of GCS score in protocol and severity of anatomical injury on brain CT, but not severity of extracranial injury (though second analysis excludes those with non-head AIS scores >3). Included given limited other evidence available.
Outcomes and effect sizes	Note that data is reported as OR (95% confidence intervals) in the paper, which is extracted below. **<u>Diabetes insipidus – time-point assessed at unclear (mean time from admission to ICU to onset of diabetes insipidus was 1.2 (1.7) days)</u>** *Whole cohort, n=425 analysed* **OR 3.36 (95% CI 1.64 to 7.18) for GCS ≤8 vs. GCS >8, P-value 0.0012** **OR 2.60 (95% CI 1.21 to 5.97) for head AIS >3 vs. head AIS = 3, P-value 0.0178** *Excluding patients with chest, abdomen and extremity AIS >3, n=397 analysed* **OR 3.92 (95% CI 1.84 to 8.86) for GCS ≤8 vs. GCS >8, P-value <0.0001** **OR 2.87 (95% CI 1.30 to 6.89) for head AIS >3 vs. head AIS = 3, P-value 0.0446**

Reference	Hadjizacharia 2008[2]
	Criteria for diabetes insipidus were urine output 300 mL/hour for more than 3 hours, hypernatremia, hyperosmolarity, and the use of Desmopressin Acetate. Duration of treatment with Desmopressin Acetate was 1.6 (1.3) days and 1.7 (1.3) days for those with isolated head injury.
Comments	**Risk of bias (differences across risk factor/subgroup combinations indicated below):** 1. Study participation — MODERATE 2. Study attrition — MODERATE 3. Prognostic factor measurement — LOW (for GCS) or MODERATE (for head AIS >3) 4. Outcome Measurement — MODERATE 5. Study confounding — LOW (for subgroup excluding extracranial AIS >3) or MODERATE (for overall cohort with no exclusions based on extracranial AIS) 6. Statistical analysis — MODERATE OVERALL RISK OF BIAS — HIGH (for all) **Indirectness (applies to all risk factors):** • Population – not stratified by severity of TBI based on GCS as in the review protocol and mild-severe included as a single group for analysis. Also limits to those with head AIS score of at least 3 and adults and children combined but mean age consistent with adult population.

Reference	Klose 2007[3]
Study type and analysis	Cross-sectional cohort study, prospective recruitment (some information obtained retrospectively from records) Logistic regression analyses conducted to analyse association between pituitary insufficiency and potential predictive factors. Differences considered significant when P<0.05. All direct effects retained in the model.
Number of participants and characteristics	N=156 invited, with n=104 finally included (n=104 with data for TBI severity and n=27 with data for intracranial pressure) • Mild GCS (13-15), n=44 • Moderate GCS (9-12), n=20 • Severe GCS (3-8), n=40 • Intracranial pressure >15 mmHg for more than 24 h, n=15 • Normal intracranial pressure (≤15 mmHg), n=12 **Inclusion criteria:** patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time. **Exclusion criteria:** doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge. **Population characteristics:** given separately for n=16 with and n=88 without hypopituitarism (continuous values are median (range)) • Age: 56 (23-64) vs. 39 (18-64) years • Male sex, 56.3% vs. 78.4% • GCS: ○ Mild, 13.0% vs. 48.0% (GCS 13-15) ○ Moderate, 6.0% vs. 21.0% (GCS 9-12) ○ Severe, 81.0% vs. 31.0% (GCS < 9) • Hospital length of stay: 54 (5-220) vs. 9 (1-270) days • Abnormal CT, 100.0% (16/16) vs. 84.0% (71/85)

Reference	Klose 2007[3]
	• Intracranial pressure >15 mmHg, 75.0% (6/8) vs. 32.0% (6/19) • Intubation >1 day, 63.0% (10/16) vs. 22.0% (19/78) • Endocrine measures: ○ IGF-I: 151 (95 to 241) vs. 181 (56 to 417) ng/ml ○ IGF-I (SDS): -0.6 (-2.1 to 1.6) vs. -0.4 (-3.8 to 3.0) ○ IGFBP-3: 3156 (1953 to 4161) vs. 3053 (1673 to 5517) ng/ml ○ Baseline cortisol: 298 (13 to 477) vs. 402 (104 to 814) nmol/l ○ TSH: 1.4 (0.7 to 4.6) vs. 1.5 (0.1 to 6.3) mIU/l ○ FT4: 15.0 (5.3 to 20.2) vs. 16.5 (10.6 to 25.4) pmol/l ○ Testosterone (men): 13 (0.4 to 23.0) vs. 20.0 (9.6 to 36.0) nmol/l ○ Luteinising hormone: 2.8 (0.2 to 6.9) vs. 4.3 (1.6 to 11.0) IU/l ○ Oestradiol: ▪ Pre-menopausal: 0.14 (0.11 to 0.16) vs. 0.29 (0.04 to 1.45) nmol/l ▪ Post-menopausal: 0.05 (0.04 to 0.08) vs. 0.05 (0.02 to 0.16) nmol/l ○ Follicle-stimulating hormone: ▪ Pre-menopausal: 7.1 (6.6 to 7.6) vs. 4.1 (1.9 to 11.9) IU/l ▪ Post-menopausal: 64.0 (42.0 to 116.0) vs. 59.0 (48.0 to 200.0) IU/l *Additional characteristics given for overall population (n=104)* • Cause of injury: ○ Road accident, 63.0% ○ Fall, 28.0% ○ Assault, 8.0% ○ Gunshot, 1.0% **Population source:** consecutive series of patients matching inclusion criteria admitted to Departments of Neurosurgery at University Hospital of Copenhagen at Rigshospitalet and Glostrup County Hospital from October 2003 to May 2005.
Prognostic variables	Mild GCS (13-15) (referent) Moderate GCS (9-12) Severe GCS (3-8)

Reference	Klose 2007[3]
	Intracranial pressure >15 mmHg for more than 24 h Normal intracranial pressure (≤15 mmHg) (referent) GCS was used to define TBI severity based on the first GCS score after basic resuscitation. Intracranial pressure was defined as abnormal if it was elevated (≥15 mmHg) for >24 h (n=17 patients did not have data for this as they were not monitored for intracranial pressure).
Confounders	Assume full list of those included provided in table 5: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI. Is unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results. Has likely adjusted for key confounder of GCS score in protocol, but not: severity of anatomical injury on brain CT or severity of extracranial injury. Included given limited other evidence available.
Outcomes and effect sizes	Note that data is reported as OR (95% confidence intervals) in the paper, which is extracted below. **Hypopituitarism – measured close to admission but only confirmed by re-testing at 1-3 months** **OR 1.4 (95% CI 0.1 to 17.7) for moderate vs. mild TBI based on GCS** **OR 8.0 (95% CI 1.5 to 43.2) for severe vs. mild TBI based on GCS** **OR 6.4 (95% CI 0.4 to 93.9) for intracranial pressure >15 mmHg for 24 h vs. normal intracranial pressure** Anterior pituitary function assessed between 8.00 and 10.00 am after an overnight fast. Patients rested 15-30 min prior to testing, after inserting large indwelling catheter in large forearm vein, and baseline samples taken for analysis of TSH, free T4, FSH, total testosterone (in men) oestradiol (in women), prolactin, total cortisol, growth hormone, IGF-I and IGFBP-3. No patient received any hormonal treatment at time of testing. Insulin tolerance test performed in all patients apart from those with overt contraindications such as epilepsy or ischaemic vascular disease (n=7 each). Soluble insulin administered by IV to induce adequate hypoglycaemia (blood glucose <2.0 mmol/l with relevant glycaemic symptoms). Blood collected at -15, 0, 15, 30, 45, 60, 75 and 90 min for measurement of serum growth hormone and cortisol. No patients given IV or oral glucose during the test. Arginine (0.5 g/kg max 30 g, infused from 0-30 min) + GHRH (0.1 μg/kh IV at 0 min) test performed in all patients with contraindications to insulin tolerance test with sampling at same time-points for growth hormone. In these patients, hypothalamic-pituitary-adrenocortical (HPA) axis evaluated by ACTH test, with 250 μg ACTH IV delivered. Blood collected at baseline and 30 min. Plasma levels of each hormone analysed by electrochemiluminescence immunoassay. HPA axis deficiency defined as peak or 30-min cortisol <500 nmol/l in response to insulin tolerance test and ACTH test, respectively. Secondary hypothyroidism suspected in patients

Reference	Klose 2007[3]
	with subnormal serum free-T4 (<12 pmol/l) associated with inappropriately low TSH. In these, reassessment of free T4 and TT4 and measurement of thyroid hormone binding globulin and a resin T3 test added to improve accuracy. Hypogonadotropic hypogonadism in postmenopausal women defined as inappropriately low gonadotrophic for age; in premenopausal women presence of amenorrhoea or oligomenorrhea associated with persistently low oestradiol and inappropriately low gonadotrophins; and in men as low serum total testosterone (<10 mmol/l) associated with inappropriately low luteinising hormone. Where hypogonadism was suspected in men, evaluation was repeated with measurement of inhibin B and SHBG to improve accuracy. Severe growth hormone deficiency defined as peak growth hormone <7.8 mU/l (3 µg/l) in response to hypoglycaemia and as peak growth hormone <23 mU/l (9 µg/l) in response to arginine GHRH. Partial growth hormone deficiency defined by peak growth hormone response ≤13 mU/l (5 µg/l) but ≥7.8 mU/l (3 µg/l) in response to insulin tolerance test or ≤43 mU/l (16.5 µg/l) but ≥23 mU/l (9 µg/l) in response to arginine GHRH. Hyperprolactinaemia defined as prolactin >510 miU/l in absence of macroprolactinaemia. ADH deficiency considered in cases of reported polyuria and polydipsia and diagnosed in patients by insufficient water deprivation test. Insufficiencies all confirmed by re-testing within 1-3 months.
Comments	**Risk of bias (differences between risk factors indicated):** 1. Study participation — LOW 2. Study attrition — MODERATE 3. Prognostic factor measurement — LOW (for GCS) and MODERATE (for intracranial pressure) 4. Outcome Measurement — MODERATE 5. Study confounding — MODERATE 6. Statistical analysis — LOW OVERALL RISK OF BIAS — HIGH **Indirectness (applies to all risk factors):** • Population – not stratified by severity of TBI based on GCS as in the review protocol and mild-severe included as a single group for analysis

Reference	Yang 2016[5]
Study type and analysis	Retrospective study

Reference	Yang 2016[5]
	Cox proportional hazards models used to compute HRs and 95% confidence intervals after adjustment for comorbidities and sociodemographic characteristics.
Number of participants and characteristics	N=31,389 with TBI (unclear if all analysed in terms of HRs) • Male gender, n=19,024 (assumed as number analysed not clear for adjusted results) • Female gender, n=12,365 (assumed as number analysed not clear for adjusted results) • Diabetes mellitus, n=2735 (assumed as number analysed not clear for adjusted results) • No diabetes mellitus, n=28,654 (assumed as number analysed not clear for adjusted results) • Mild head injury based on ICD-9 code 850, n=11,063 (assumed as number analysed not clear for adjusted results) • Intracranial haemorrhage based on ICD-9 codes 851-854, n=14,940 (assumed as number analysed not clear for adjusted results) • Skull bone fracture based on ICD-9 codes 800-804, n=5386 (assumed as number analysed not clear for adjusted results) **Inclusion criteria:** patients suffering TBI (ICD-9 codes 800-804, 850-854) between 1996 and 2009. **Exclusion criteria:** endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data **Population characteristics:** given separately for whole cohort of n=31,389 (continuous values are mean (SD)) • Age: 39.75 (19.18) years o <18 years, 10.4% o 18-45 years, 52.5% o >45 years, 37.1% • Male sex, 60.6% • Diabetes mellitus, 8.7% • Hypertension, 19.5% • Heart disease, 8.6% • Arrhythmia, 4.9%

Reference	Yang 2016[5]
	• TBI (based on TBI codes): ○ Mild head injury, 35.2% ○ Intracranial haemorrhage, 47.6% ○ Skull bone fracture, 17.2% **Population source:** data collected retrospectively from National Health Insurance programme set up by Taiwanese government in March 1995. Provides general health insurance coverage to most of Taiwanese population. National Health Insurance Research Database (NHIRD) contains registration files and original reimbursement claims data. Contains medical information, including data on medical care facilities and specialities, information on prescriptions, operations and examinations, patient sex and birth date, date of visit or hospitalisation, transfer identification number and diagnoses coded in ICD-9 format. Study included those matching TBI criteria between 1996 and 2009.
Prognostic variables	Male gender Female gender *Unclear which one used as referent and unable to work out from other data in paper* Diabetes mellitus No diabetes mellitus (referent) Mild head injury based on ICD-9 code 850 Intracranial haemorrhage based on ICD-9 codes 851-854 Skull bone fracture based on ICD-9 codes 800-804 *(each of above three groups vs. those without that feature)* Clinical and investigation data obtained from medical records as described under population source above.
Confounders	Factors included in multivariate analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture). Has adjusted to some extent for key confounder of severity of injury on brain CT scan but unclear if based on CT for all patients, has not adjusted for GCS score severity or severity of extracranial injury. Included given limited other evidence available.
Outcomes and effect sizes	Note that data is reported as HR (95% confidence intervals) in the paper, which is extracted below. **Post-traumatic pituitary dysfunction – 1 year follow-up time-point**

Reference	Yang 2016[5]
	HR 0.16 (95% CI 0.099 to 0.252) for gender (unclear if male or female used as referent), P-value <0.001 **HR 2.41 (95% CI 1.207 to 4.793) for diabetes mellitus vs. no diabetes mellitus, P-value 0.013** **HR 1.78 (95% CI 0.965 to 3.281) for mild head injury vs. not mild head injury diagnosis (ICD-9 code), P-value not significant** **HR 1.76 (95% CI 1.007 to 3.064) for intracranial haemorrhage vs. not intracranial haemorrhage diagnosis (ICD-9 code), P-value 0.047** **HR 3.77 (95% CI 1.942 to 7.327) for skull bone fracture vs. not skull bone fracture diagnosis (ICD-9 code), P-value <0.001** **<u>Post-traumatic pituitary dysfunction – 5 year follow-up time-point</u>** **HR 0.11 (95% CI 0.086 to 0.135) for gender (unclear if male or female used as referent), P-value <0.001** **HR 2.12 (95% CI 1.517 to 2.955) for diabetes mellitus vs. no diabetes mellitus, P-value <0.001** **HR 1.41 (95% CI 1.066 to 1.853) for mild head injury vs. not mild head injury diagnosis (ICD-9 code), P-value 0.016** **HR 1.46 (95% CI 1.141 to 1.854) for intracranial haemorrhage vs. not intracranial haemorrhage diagnosis (ICD-9 code), P-value 0.002** **HR 1.41 (95% CI 0.900 to 2.208) for skull bone fracture vs. not skull bone fracture diagnosis (ICD-9 code), P-value not significant** Enrolled study subjects followed up until death or end of 2009. Following ICD-9 code used to define presence of pituitary dysfunction: 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during the study period.
Comments	**Risk of bias (applies to all risk factors):** 1. Study participation — LOW 2. Study attrition — MODERATE 3. Prognostic factor measurement — MODERATE 4. Outcome Measurement — HIGH 5. Study confounding — HIGH 6. Statistical analysis — LOW OVERALL RISK OF BIAS — HIGH **Indirectness (applies to all risk factors):** • Population – not stratified by severity of TBI based on GCS as in the review protocol and mild-severe included as a single group for analysis (GCS not reported in paper but no exclusions based on injury severity reported)

Reference	You 2019[6]
Study type and analysis	Retrospective study Binary logistic regression analysis performed to determine independent risk factors for TBI-induced hypopituitarism. Significance determined at P<0.05.
Number of participants and characteristics	N=193 eligible and analysed • Intracranial hypertension, n=108 • No intracranial hypertension, n=85 • Mild GCS (13-15), n=98 • Moderate GCS (9-12), n=49 • Severe GCS (3-8), n=46 **Inclusion criteria:** TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation **Exclusion criteria:** pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records. **Population characteristics:** given separately for n=33 with and n=160 without hypopituitarism (continuous values are mean (SD)) • Age: 54.6 (11.7) years • Male sex, 66.7% vs. 66.3% • GCS at admission: 9.1 (3.5) vs. 11.8 (3.6) • Length of ICU stay: 8.7 (5.5) vs. 3.3 (4.6) days • Length of total hospital stay: 28.7 (20.1) vs. 21.0 (15.8) days • Secondary epilepsy, 9.1% vs. 9.4% • Brain imaging: ○ Midline shift, 51.5% vs. 34.4% ○ Basal cistern compression, 12.1% vs. 13.1% ○ Epidural haematoma, 24.2% vs. 16.3% ○ Subdural haematoma, 54.5% vs. 43.8%

Reference	You 2019[6]
	○ Basal fracture, 42.4% vs. 44.4% ○ Traumatic subarachnoid haemorrhage, 54.5% vs. 55.6% ○ Diffuse brain oedema, 12.1% vs. 8.8% • Intracranial hypertension, 81.8% vs. 50.6% • Surgical intervention, 42.4% vs. 32.5% *Additional characteristics given for overall population (n=193)* • Overall pituitary axes dysfunction, 17.1% ○ Hypothyroidism, 13.0% ○ Hypogonadism, 3.6% ○ Growth hormone deficiency, 2.6% ○ ACTH deficiency, 2.1% ○ Hyperprolactinaemia, 0.0% • Two pituitary axes dysfunction, 4.7% • Cause of brain injury: ○ Traffic accident, 47.1% ○ Falls, 35.8% ○ Other, 17.1% • Interval between brain injury and evaluation (median, IQR): 7.5 (3-34) days **Population source:** retrospective review of medical records between for patients admitted following TBI between January 2014 and December 2016 to Department of Neurosurgery at First Affiliated Hospital of Zhejiang University School of Medicine.
Prognostic variables	Intracranial hypertension No intracranial hypertension (referent) Mild GCS (13-15) (referent) Moderate GCS (9-12)

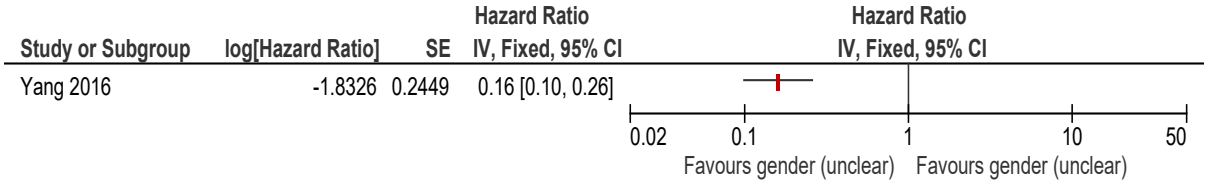
Reference	You 2019[6]
	Severe GCS (3-8) Severity of brain injury (GCS) and intracranial pressure was extracted from case records alongside other clinical information (age, sex, BMI, cause of trauma, pre-existing endocrinopathy, medication use, secondary epilepsy, surgical intervention, length of ICU and hospital stay). Intracranial hypertension defined as: intracranial pressure ≥20 mmHg. Severity of TBI assessed according to GCS at admission and post-resuscitation. Neuroimaging of patients included CT and MRI which were reviewed by two investigators blinded to patient neuroendocrine functions.
Confounders	Assume full list of those included provided in table 4 as includes even those with lower P-values: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS). Has adjusted for key confounder of GCS score in protocol, but not: severity of anatomical injury on brain CT or severity of extracranial injury. Included given limited other evidence available.
Outcomes and effect sizes	Note that data is reported as OR (95% confidence intervals) in the paper, which is extracted below. **<u>Hypopituitarism – median (IQR) interval between brain injury and evaluation was 7.5 (3-34) days (re-testing to confirm at 1-3 months)</u>** **OR 3.206 (95% CI 1.145 to 8.975) for intracranial hypertension vs. no intracranial hypertension, P-value 0.027, SE 0.525** **OR 0.471 (95% CI 0.125 to 1.767) for moderate GCS vs. mild GCS, P-value 0.264, SE 0.675** **OR 0.839 (95% CI 0.172 to 4.080) for severe GCS vs. mild GCS, P-value 0.828, SE 0.807** Within the department, moderate-severe TBI or patients with mild TBI requiring hospitalisation for at least 24 h were screened for pituitary function. Hormone levels measured in laboratory of the hospital. Measured using electrochemiluminescence. Pituitary-adrenal axis assessed by measuring cortisol concentration. Basal cortisol level measured early in the morning (8 am) after an overnight fast. Adrenocorticotropic hormone deficiency defined as: peak cortisol in stimulation test <500 nmol/L (18 µg/dL) or basal cortisol <100 nmol/L (3.6 µg/dL) if no stimulation test was performed. Free thyroxine (FT4) and thyroid-stimulating hormone (TSH) were used to evaluate pituitary-thyroid axis. Hypothyroidism defined by low serum FT4 <12 pmol/L (0.93 ng/dL) without elevation in serum TSH. Growth hormone/insulin-like factor-1 (GH/IGF-1) axis evaluated with basal insulin tolerance test. GH deficiency defined with basal IGF-1 below local age and sex specific reference value (IGF-1 SDS <-2.00) or peak GF <3 ng/ml after stimulation for all patients. However, insulin tolerance test should induce hypoglycaemia which may be dangerous to patients with epilepsy and heart disease. In addition, it is challenging to perform this test in the acute phase after brain injury; therefore, this test was usually not used. Pituitary-gonadal axis assessed with morning testosterone or random estradiol, luteinising hormone, follicle-stimulating hormone. Hypogonadism defined as testosterone <9.9 nmol/L (2.85 ng/ml) in men. In women, hypogonadism defined as amenorrhea and/or

Reference	You 2019[6]
	luteinising hormone ≤1.7 U/L and follicle-stimulating hormone ≤1.5 U/L (at pre-menopause stage) OR luteinising hormone ≤15 U/L and/or follicle-stimulating hormone ≤15 U/L (at post-menopausal stage). Insufficiencies all confirmed by retests within 1-3 months. Lactotroph axis assessed by prolactin and hyperprolactinaemia defined as prolactin level >20 ng/ml for males and >25 ng/ml for females.
Comments	**Risk of bias (applies to all risk factors):** 1. Study participation — LOW 2. Study attrition — MODERATE 3. Prognostic factor measurement — LOW 4. Outcome Measurement — MODERATE 5. Study confounding — MODERATE 6. Statistical analysis — LOW OVERALL RISK OF BIAS — HIGH **Indirectness (applies to all risk factors):** • Population – not stratified by severity of TBI based on GCS as in the review protocol and mild-severe included as a single group for analysis

Appendix E – Forest plots

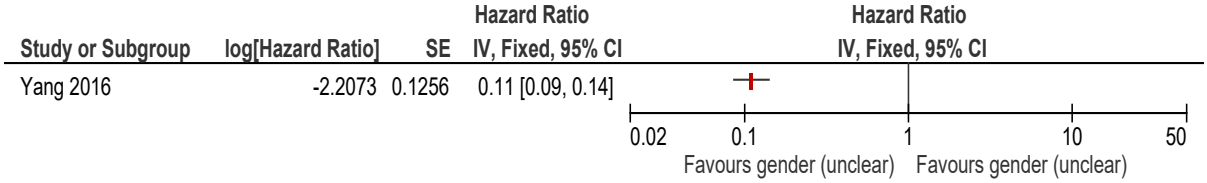
E.1 Adults – Gender

Figure 2: Gender (unclear if male or female used as referent) for predicting post-traumatic pituitary dysfunction at 1 year



Both sides of the forest plot are labelled 'favours gender (unclear)' because it is unclear which gender was more predictive of traumatic pituitary dysfunction at 1 year.

Figure 3: Gender (unclear if male or female used as referent) for predicting post-traumatic pituitary dysfunction at 5 years



Both sides of the forest plot are labelled 'favours gender (unclear)' because it is unclear which gender was more predictive of traumatic pituitary dysfunction at 5 years.

E.2 Adults – GCS

Figure 4: GCS ≤8 vs. GCS >8 for predicting diabetes insipidus – mean time from admission to ICU to onset of diabetes insipidus was 1.2 (1.7) days

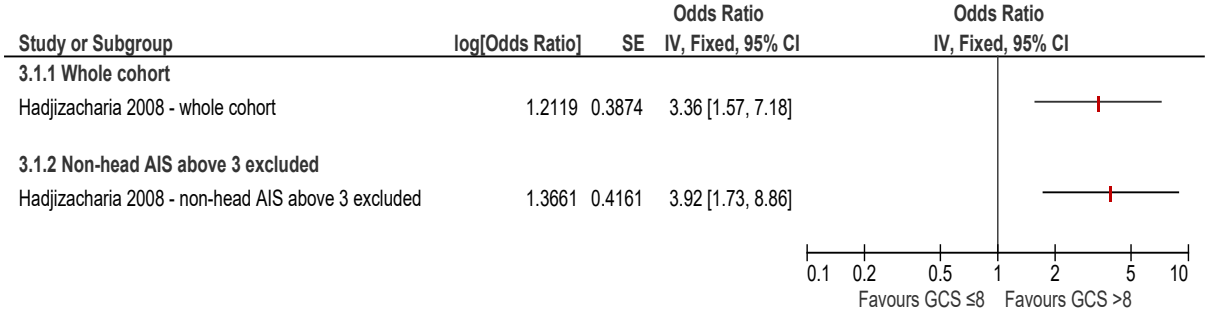
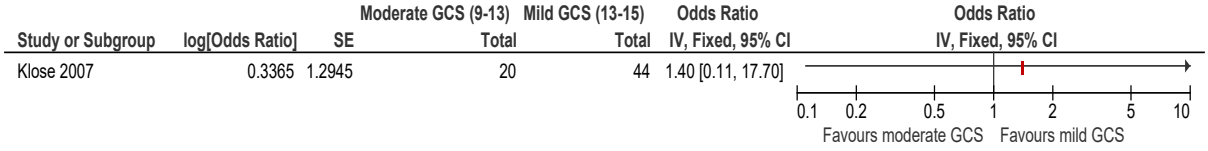
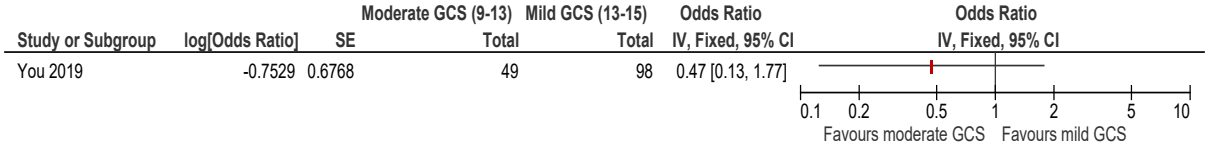


Figure 5: Moderate (GCS 9-12) vs. mild (GCS 13-15) severity for predicting hypopituitarism – measured close to admission but results confirmed by re-testing at 1-3 months



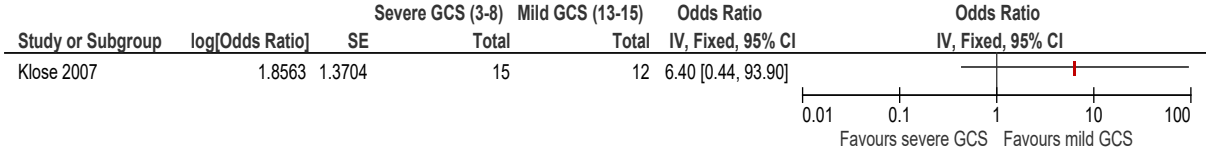
7

Figure 6: Moderate (GCS 9-12) vs. mild (GCS 13-15) severity for predicting hypopituitarism – median interval between brain injury and evaluation was 7.5 (IQR 3-34) days but results confirmed by re-testing at 1-3 months



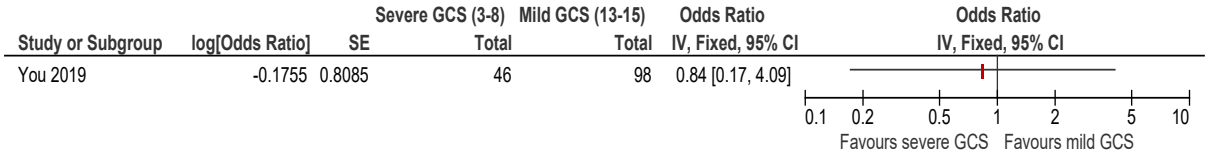
8

Figure 7: Severe (GCS 3-8) vs. mild (GCS 13-15) severity for predicting hypopituitarism – measured close to admission but results confirmed by re-testing at 1-3 months



9

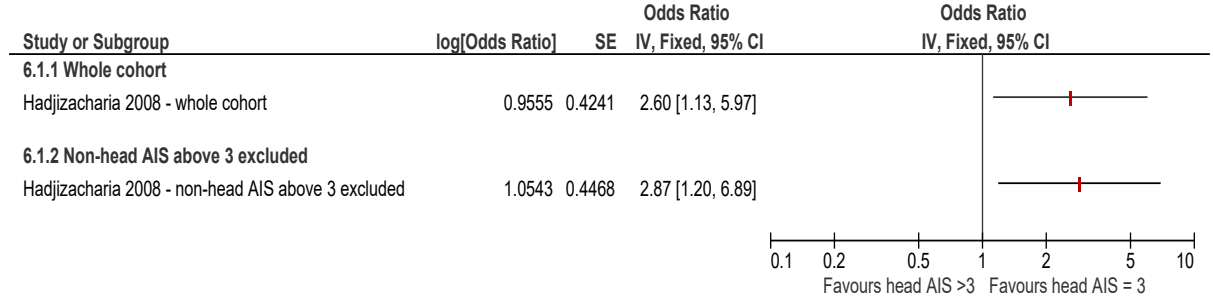
Figure 8: Severe (GCS 3-8) vs. mild (GCS 13-15) severity for predicting hypopituitarism – median interval between brain injury and evaluation was 7.5 (IQR 3-34) days but results confirmed by re-testing at 1-3 months



10

E1.3 Adults – Severity based on CT

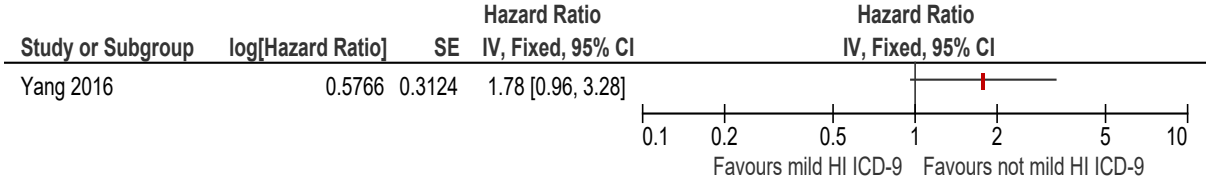
Figure 9: Head AIS >3 vs. = 3 for predicting diabetes insipidus – mean time from admission to ICU to onset of diabetes insipidus was 1.2 (1.7) days



12

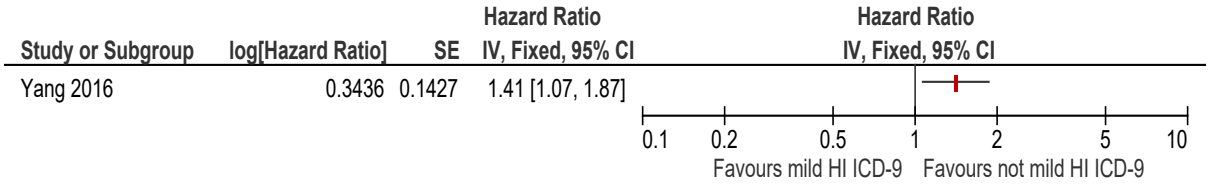
E1.4 Adults – Injury severity based on ICD-9 code

Figure 10: Mild head injury vs. not mild based on ICD-9 code for predicting post-traumatic pituitary dysfunction at 1 year



14

Figure 11: Mild head injury vs. not mild based on ICD-9 code for predicting post-traumatic pituitary dysfunction at 5 years



15

Figure 12: Intracranial haemorrhage vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction at 1 year

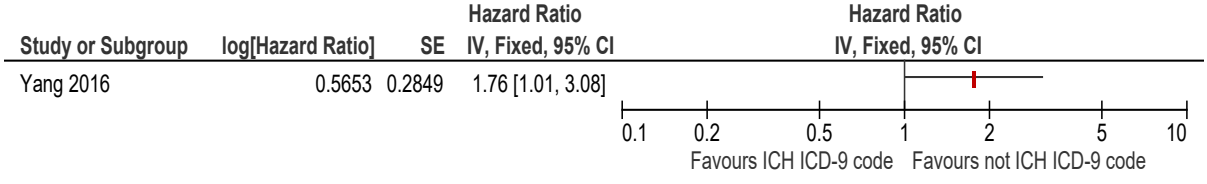


Figure 13: Intracranial haemorrhage vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction at 5 years

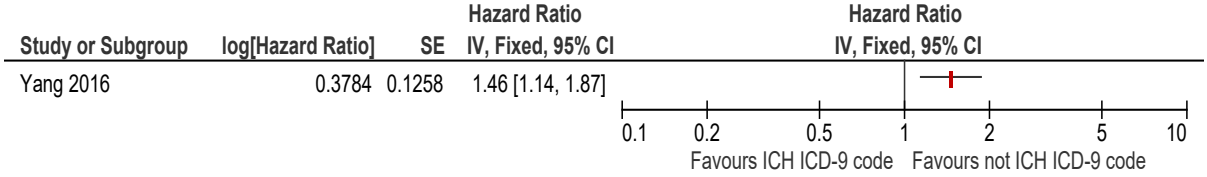


Figure 14: Skull bone fracture vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction at 1 year

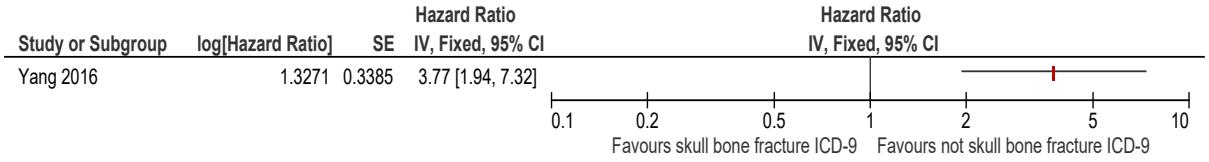
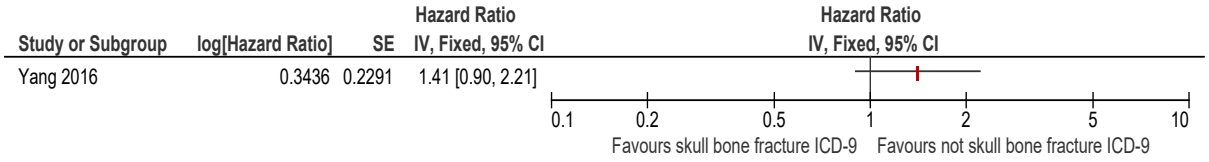


Figure 15: Skull bone fracture vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction at 5 years



E.5 Adults – Presence vs. absence of intracranial hypertension/abnormal intracranial pressure

Figure 16: Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg) for predicting hypopituitarism – median interval between brain injury and evaluation was 7.5 (IQR 3-34) days but results confirmed by re-testing at 1-3 months

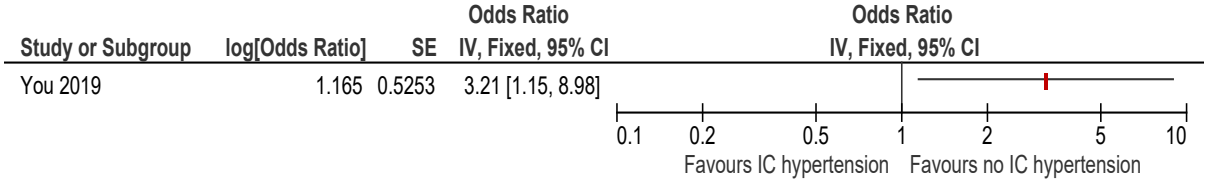
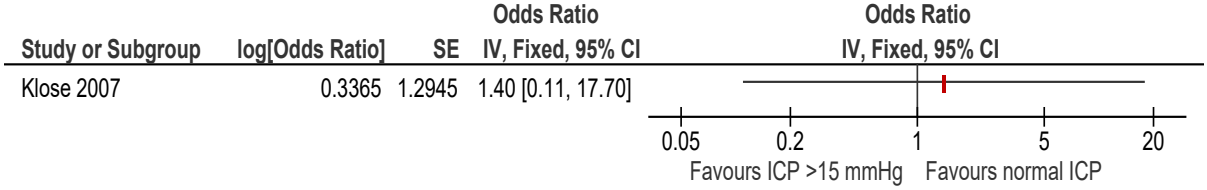


Figure 17: Intracranial pressure >15 mmHg for at least 24 h vs. normal pressure for predicting hypopituitarism – measured close to admission but results confirmed by re-testing at 1-3 months



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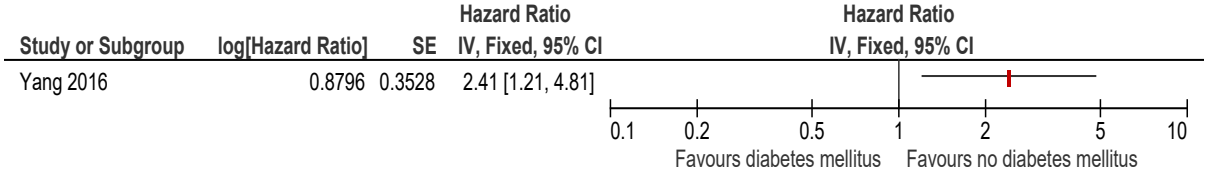
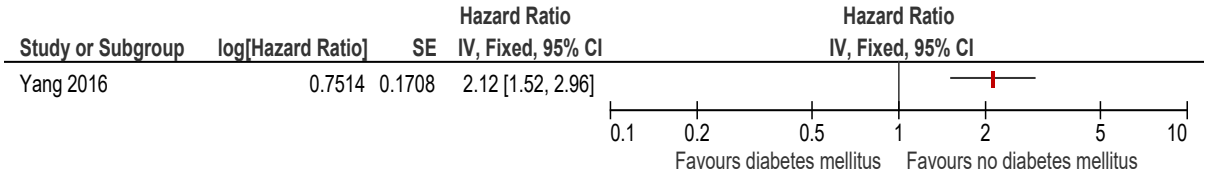
E.6 Adults – Presence vs. absence of predisposing conditions

Figure 18: Diabetes mellitus vs. no diabetes mellitus for predicting post-traumatic pituitary dysfunction at 1 year



26

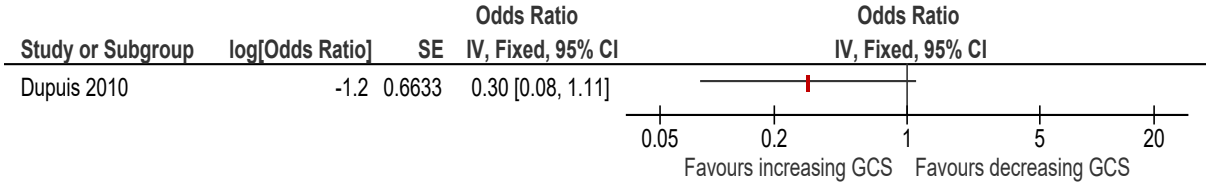
Figure 19: Diabetes mellitus vs. no diabetes mellitus for predicting post-traumatic pituitary dysfunction at 5 years



27

E.7 Children – GCS

Figure 20: GCS as a continuous variable (post-resuscitation GCS) for predicting secondary adrenal insufficiency – assessed at 2-3 days post-admission



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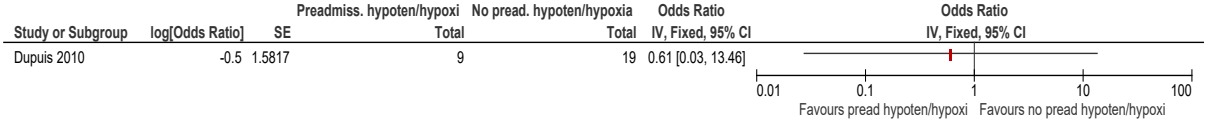
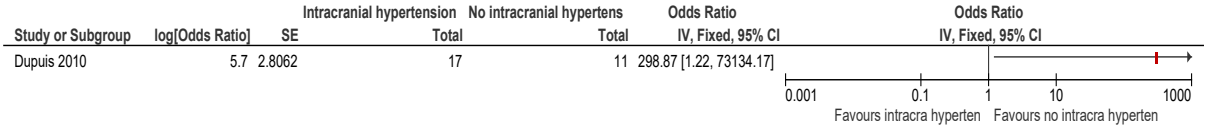
E8 Children – Presence vs. absence of preadmission hypoxia or hypotension

Figure 21: Presence of preadmission hypoxia (defined as SaO2 <90%) or hypotension [defined as systolic blood pressure lower than 70 mmHg + (2x age in years)] for predicting secondary adrenal insufficiency – assessed at 2-3 days post-admission



E9 Children – Presence vs. absence of intracranial hypertension

Figure 22: Presence of intracranial hypertension (intracranial pressure ≥20 mmHg) for predicting secondary adrenal insufficiency – assessed at 2-3 days post-admission



Appendix F – GRADE tables

F.1 Adults – gender

Table 18: Clinical evidence profile: Gender (unclear if male or female used as referent)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Gender (unclear if male or female used as referent and could not work out from other data in paper) for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) at 1 year – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 0.16 (0.10 to 0.26)	VERY LOW
Gender (unclear if male or female used as referent and could not work out from other data in paper) for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) at 5 years – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 0.11 (0.09 to 0.14)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately

F.2 Adults – GCS

able 19: Clinical evidence profile: GCS ≤8 vs. GCS >8

Quality assessment							Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Effect (95% CI)**	
GCS ≤8 vs. GCS >8 for predicting diabetes insipidus (criteria were urine output 300 mL/hour for more than 3 hours, hypernatremia, hyperosmolarity, and the use of Desmopressin Acetate) at mean time from admission to ICU to onset of diabetes insipidus 1.2 (1.7) days – (admitted to surgical ICU unit with head AIS ≥3 including blunt or penetrating injuries; mean age 37 years; 41.7% mild injury, 15.8% with moderate injury and 42.4% with severe injury based on GCS – exclusion criteria not reported) **MV analysis: age <15 years vs. 15-55 years; mechanism of injury (blunt vs. penetrating); systolic blood pressure <90 vs. ≥90 mmHg; Injury Severity Score <16 vs. ≥16; GCS ≤8 vs. >8; head AIS >3 vs. ≤3; face AIS >3 vs. ≤3; oedema yes vs. no; head fracture yes vs. no; subarachnoid haemorrhage yes vs. no; subdural haemorrhage yes vs. no; vault head fracture yes vs. no; intraparenchymal haemorrhage yes vs. no; intraventricular haemorrhage yes vs. no; pneumocephaly yes vs. no; and shift yes vs. no.**								
1 Hadjizacharia 2008[2]	Cohort study	very serious[1,2]	no serious inconsistency	very serious[3]	no serious imprecision	none	Adjusted OR: *Whole cohort:* 3.36 (1.57 to 7.18) *Subgroup with non-head AIS >3 excluded:* 3.92 (1.73 to 8.86)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study participation, study attrition, outcome measurement, confounding (for whole cohort only, not subgroup excluding those with non-head AIS >3) and statistical analysis/selecting reporting domains
[3] Downgraded by 2 increments for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately. Also only includes those with a head AIS score >3 which may limit the population compared to those seen in practice.

Table 20: Clinical evidence profile: Moderate (GCS 9-12) vs. mild (GCS 13-15) severity

Quality assessment	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Moderate (GCS 9-12) vs. mild (GCS 13-15) severity for predicting hypopituitarism (deficiency in hypothalamic-pituitary-adrenal axis, secondary hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency) when measured close to admission with results confirmed by re-testing at 1-3 months - (patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time; median age 56 years in those with outcome and 39 years in those without outcome; 13.0% vs. 48.0% mild GCS, 6.0% vs. 21.0% moderate GCS and 81.0% vs. 31.0% severe GCS – exclusion criteria were doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge) **MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI – *unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results***							
1 Klose 2007[3]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 1.40 (0.11 to 17.70)	VERY LOW
Moderate (GCS 9-12) vs. mild (GCS 13-15) severity for predicting hypopituitarism (adrenocorticotropic hormone deficiency, hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia) at median interval between brain injury and evaluation 7.5 (IQR 3-34) days with results confirmed by re-testing at 1-3 months - (TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation; mean age ~55 years; 51% mild GCS, 25% moderate GCS and 24% severe GCS – exclusion criteria were pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records) **MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS)**							
1 You 2019[6]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 0.47 (0.13 to 1.77)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

Table 21: Clinical evidence profile: Moderate (GCS 3-8) vs. mild (GCS 13-15) severity

Quality assessment	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Severe (GCS 3-8) vs. mild (GCS 13-15) severity for predicting hypopituitarism (deficiency in hypothalamic-pituitary-adrenal axis, secondary hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency) when measured close to admission with results confirmed by re-testing at 1-3 months - (patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time; median age 56 years in those with outcome and 39 years in those without outcome; 13.0% vs. 48.0% mild GCS, 6.0% vs. 21.0% moderate GCS and 81.0% vs. 31.0% severe GCS – exclusion criteria were doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge) **MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI – *unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results***							
1 Klose 2007[3]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 6.40 (0.44 to 93.90)	VERY LOW
Severe (GCS 3-8) vs. mild (GCS 13-15) severity for predicting hypopituitarism (adrenocorticotropic hormone deficiency, hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia) at median interval between brain injury and evaluation 7.5 (IQR 3-34) days with results confirmed by re-testing at 1-3 months - (TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation; mean age ~55 years; 51% mild GCS, 25% moderate GCS and 24% severe GCS – exclusion criteria were pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records) **MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS)**							
1 You 2019[6]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 0.84 (0.17 to 4.09)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

F23 Adults – severity based on CT

Table 22: Clinical evidence profile: Head Abbreviated Injury Scale (AIS) score >3 vs. = 3

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Head AIS >3 vs. = 3 for predicting diabetes insipidus (criteria were urine output 300 mL/hour for more than 3 hours, hypernatremia, hyperosmolarity, and the use of Desmopressin Acetate) at mean time from admission to ICU to onset of diabetes insipidus 1.2 (1.7) days – (admitted to surgical ICU unit with head AIS ≥3 including blunt or penetrating injuries; mean age 37 years; 41.7% mild injury, 15.8% with moderate injury and 42.4% with severe injury based on GCS – exclusion criteria not reported) **MV analysis: age <15 years vs. 15-55 years; mechanism of injury (blunt vs. penetrating); systolic blood pressure <90 vs. ≥90 mmHg; Injury Severity Score <16 vs. ≥16; GCS ≤8 vs. >8; head AIS >3 vs. ≤3; face AIS >3 vs. ≤3; oedema yes vs. no; head fracture yes vs. no; subarachnoid haemorrhage yes vs. no; subdural haemorrhage yes vs. no; vault head fracture yes vs. no; intraparenchymal haemorrhage yes vs. no; intraventricular haemorrhage yes vs. no; pneumocephaly yes vs. no; and shift yes vs. no.**								
1 Hadjizacharia 2008[2]	Cohort study	very serious[1,2]	no serious inconsistency	very serious[3]	no serious imprecision	none	Adjusted OR: *Whole cohort:* 2.60 (1.13 to 5.97) *Subgroup with non-head AIS >3 excluded:* 2.87 (1.20 to 6.89)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, confounding (for whole cohort only, not subgroup excluding those with non-head AIS >3) and statistical analysis/selecting reporting domains
[3] Downgraded by 2 increments for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately. Also only includes those with a head AIS score >3 which may limit the population compared to those seen in practice.

F24 Adults – injury severity based on ICD-9 code

Table 23: Clinical evidence profile: Mild head injury vs. not mild based on ICD-9 code

Quality assessment	Effect	Quality

Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Effect (95% CI)**	
Mild head injury vs. not mild based on ICD-9 code for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) at 1 year – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted HR: 1.78 (0.96 to 3.28)	VERY LOW
Mild head injury vs. not mild based on ICD-9 code for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) at 5 years – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 1.41 (1.07 to 1.87)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

Table 24: Clinical evidence profile: Intracranial haemorrhage vs. not based on ICD-9 code

Quality assessment	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Intracranial haemorrhage vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) <u>at 1 year</u> – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 1.76 (1.01 to 3.08)	VERY LOW
Intracranial haemorrhage vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) <u>at 5 years</u> – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 1.46 (1.14 to 1.87)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately

Table 25: Clinical evidence profile: Skull bone fracture vs. not based on ICD-9 code

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	

Skull bone fracture vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) <u>at 1 year</u> – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 3.77 (1.94 to 7.32)	VERY LOW
Skull bone fracture vs. not based on ICD-9 code for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) <u>at 5 years</u> – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted HR: 1.41 (0.90 to 2.21)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

F.5 Adults – presence vs. absence of intracranial hypertension/abnormal intracranial pressure

Table 26: Clinical evidence profile: Presence vs. absence of intracranial hypertension/abnormal intracranial pressure

Quality assessment							Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Effect (95% CI)**	

Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg) for predicting hypopituitarism (adrenocorticotropic hormone deficiency, hypothyroidism, growth hormone deficiency, hypogonadism or hyperprolactinaemia) at median interval between brain injury and evaluation 7.5 (IQR 3-34) days with results confirmed by re-testing at 1-3 months - (TBI admitted to Department of Neurosurgery at single hospital; aged ≥18 years; and had neuroendocrine function evaluation; mean age ~55 years; 51% mild GCS, 25% moderate GCS and 24% severe GCS – exclusion criteria were pre-existing psychiatric disorder; had previous severe head trauma or stroke; malignant disease; chronic use of glucocorticoids; pre-existing adrenal or pituitary insufficiency; and missing medical records) **MV analysis: length of ICU stay; intracranial hypertension; length of total hospital stay; and injury severity (moderate vs. mild and severe vs. mild based on GCS)**								
1 You 2019[6]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted OR: 3.21 (1.15 to 8.98)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol

Table 27: Clinical evidence profile: Intracranial pressure >15 mmHg for at least 24 h vs. normal pressure

Quality assessment							Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Effect (95% CI)**	
Intracranial pressure >15 mmHg for at least 24 h vs. normal pressure for predicting hypopituitarism (deficiency in hypothalamic-pituitary-adrenal axis, secondary hypothyroidism, hypogonadotrophic hypogonadism, growth hormone deficiency, hyperprolactinaemia or antidiuretic hormone deficiency) when measured close to admission with results confirmed by re-testing at 1-3 months - (patients with TBI (ICD-10 codes S06.0-06.9); aged 18-65 years; admitted to neurosurgery departments of two hospitals; Danish citizens living in Denmark at the time; median age 56 years in those with outcome and 39 years in those without outcome; 13.0% vs. 48.0% mild GCS, 6.0% vs. 21.0% moderate GCS and 81.0% vs. 31.0% severe GCS – exclusion criteria were doubt of diagnosis (e.g. commotio cerebri vs. alcohol intoxication); alcohol or drug abuse; psychiatric disease; previous severe head trauma or apoplexy; malignant disease; chronic use of glucocorticoids; missing medical records; unknown address; or misclassification at discharge) **MV analysis: TBI severity based on GCS (moderate or severe vs. mild); intracranial pressure abnormal; intubation >1 day; and BMI (overweight or obese vs. normal) – also said to be adjusted for gender and BMI –** ***unclear if adjusted for all of these factors or only each risk factor adjusted for gender and BMI, but describes a model in the methods suggesting multivariate results***								
1 Klose 2007[3]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 1.40 (0.11 to 17.70)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains

[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

F6 6 Adults – presence vs. absence of predisposing conditions

Table 28: Clinical evidence profile: Diabetes mellitus vs. no diabetes mellitus

Quality assessment							Effect	Quality
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations (including publication bias where possible)**	**Effect (95% CI)**	
Diabetes mellitus vs. no diabetes mellitus for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) at 1 year – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 2.41 (1.21 to 4.81)	VERY LOW
Diabetes mellitus vs. no diabetes mellitus for predicting post-traumatic pituitary dysfunction (defined by ICD-9 code 253, with at least three records of outpatient visits within 1 year or one admission diagnosis during study period) at 5 years – (patients with TBI from national database; mean age ~40 years; 35.2% mild head injury based on ICD-9 code – excluded endocrine dysfunction, stroke (ICD-9 430-438) or brain tumour (ICD-9 191, 225.01, 225.1, 225.2) diagnosed before TBI event; and subjects with data errors or missing data) **MV analysis: gender; age, diabetes mellitus, hypertension, heart disease, arrhythmia, urbanised level (2, 3 or 4), income level (New Taiwan Dollars) and TBI severity based on ICD-9 code (mild, intracranial haemorrhage or skull bone fracture)**								
1 Yang 2016[5]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted HR: 2.12 (1.52 to 2.96)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol and children and adults are included together rather than separately

F.7 Children – GCS

Table 29: Clinical evidence profile: GCS as a continuous variable (post-resuscitation GCS)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
GCS as a continuous variable (post-resuscitation GCS) for predicting secondary adrenal insufficiency (if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l) when assessed at 2-3 days post-admission - (admitted to ICU of single centre following TBI; median age 12 years in groups with and without the outcome; median GCS 7 vs. 9 in those with and without outcome, respectively – exclusion criteria were expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected) **MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).**								
1 Dupuis 2010[1]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 0.30 (0.08 to 1.11)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol.
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

F.8 Children – presence vs. absence of preadmission hypoxia or hypotension

Table 30: Clinical evidence profile: Presence vs. absence of preadmission hypoxia or hypotension

Quality assessment	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Presence vs. absence of preadmission hypoxia or hypotension for predicting secondary adrenal insufficiency (if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l) when assessed at 2-3 days post-admission - (admitted to ICU of single centre following TBI; median age 12 years in groups with and without the outcome; median GCS 7 vs. 9 in those with and without outcome, respectively – exclusion criteria were expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected) **MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).**								
1 Dupuis 2010[1]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	serious[4]	none	Adjusted OR: 0.61 (0.03 to 13.46)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol.
[4] Downgraded by 1 increment as serious imprecision was present as the confidence intervals crossed the null line (1.0)

F.9 Children – presence vs absence of intracranial hypertension

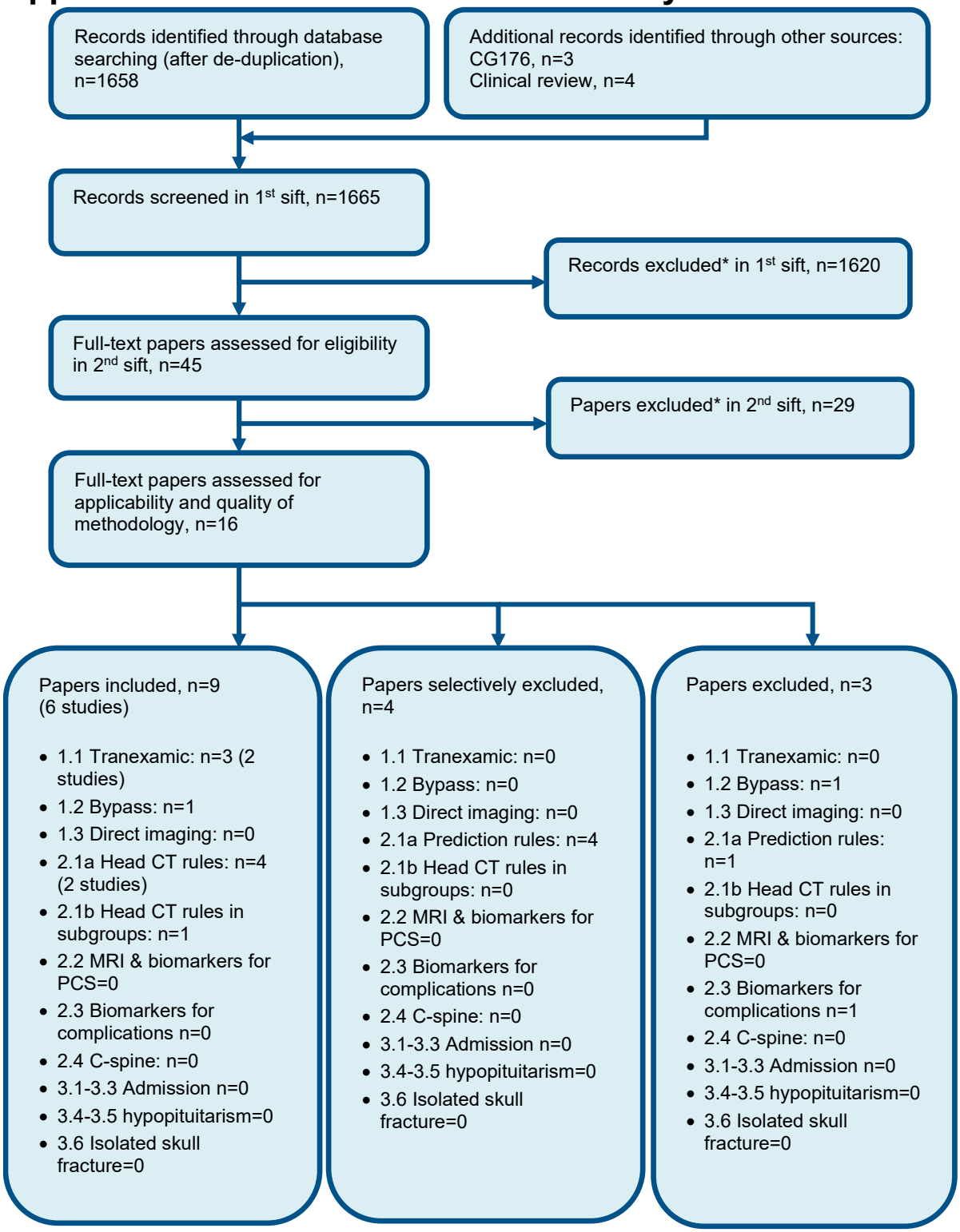
Table 31: Clinical evidence profile: Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg)

Quality assessment							Effect	Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations (including publication bias where possible)	Effect (95% CI)	
Presence vs. absence of intracranial hypertension (intracranial pressure ≥20 mmHg) for predicting secondary adrenal insufficiency (if all serial cortisol levels were below 200 nmol/l (6 µg/dl) with all ACTHs below higher limit of normal values (12 pmol/l). For those that had received etomidate, drug-induced 11b-hydroxylase deficiency was considered if 11-deoxycortisol was >8 nmol/l) when assessed at 2-3 days post-admission - (admitted to ICU of single centre following TBI; median age 12 years in groups with and without the outcome; median GCS 7 vs. 9 in those with and without outcome, respectively – exclusion criteria were expected length of stay in the unit <3 days; pre-existing adrenal or pituitary insufficiency; and inflicted TBI suspected) **MV analysis: GCS score; PRISM score; received etomidate; preadmission hypotension or hypoxia; intracranial hypertension; and intracerebral haematoma (frontal or temporal lobes).**								

1 Dupuis 2010[1]	Cohort study	very serious[1,2]	no serious inconsistency	serious[3]	no serious imprecision	none	Adjusted OR: 298.87 (1.22 to 73134.17)	VERY LOW

[1] Downgraded by 1 increment if the majority of the evidence was at moderate risk of bias, and downgraded by 2 increments if the majority of evidence was at high risk of bias
[2] Risk of bias was identified for study attrition, prognostic factor measurement, outcome measurement and study confounding domains
[3] Downgraded by 1 increment for indirectness as the population is not stratified by GCS injury severity as in the protocol.

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

None.

Appendix I – Health economic model

No original economic modelling was undertaken.

4 Appendix J – Excluded studies

5 Clinical studies

6 Table 32: Studies excluded from the clinical review

Study	Code [Reason]
Agha, A., Rogers, B., Mylotte, D. et al. (2004) Neuroendocrine dysfunction in the acute phase of traumatic brain injury. Clinical Endocrinology 60(5): 584-91	- Not a prognostic study
Agha, A., Rogers, B., Sherlock, M. et al. (2004) Anterior pituitary dysfunction in survivors of traumatic brain injury. Journal of Clinical Endocrinology & Metabolism 89(10): 4929-36	- Data not reported in an extractable format that can be analysed
Agha, A., Sherlock, M., Phillips, J. et al. (2005) The natural history of post-traumatic neurohypophysial dysfunction. European Journal of Endocrinology 152(3): 371-7	- Data not reported in an extractable format that can be analysed
Agha, A., Thornton, E., O'Kelly, P. et al. (2004) Posterior pituitary dysfunction after traumatic brain injury. Journal of Clinical Endocrinology & Metabolism 89(12): 5987-92	- Data not reported in an extractable format that can be analysed
Agrawal, M.; Varshney, T.; Sinha, V. D. (2017) Prognostic Assessment of Endocrine Disturbances in Posttraumatic Subarachnoid Hemorrhage. Indian Journal of Neurotrauma 14(2-3): 109-115	- No multivariate analysis for outcomes relevant to the review protocol
Aimaretti, G., Ambrosio, M. R., Di Somma, C. et al. (2004) Traumatic brain injury and subarachnoid haemorrhage are conditions at high risk for hypopituitarism: screening study at 3 months after the brain injury. Clinical Endocrinology 61(3): 320-6	- Not a prognostic study
Aimaretti, G., Ambrosio, M. R., Di Somma, C. et al. (2005) Hypopituitarism induced by traumatic brain injury in the transition phase. Journal of Endocrinological Investigation 28(11): 984-9	- Not a prognostic study
Aimaretti, G., Ambrosio, M. R., Di Somma, C. et al. (2005) Residual pituitary function after brain injury-induced hypopituitarism: a prospective 12-month study. Journal of Clinical Endocrinology & Metabolism 90(11): 6085-92	- No multivariate analysis for outcomes relevant to the review protocol

Study	Code [Reason]
Auble, B. A., Bollepalli, S., Makoroff, K. et al. (2014) Hypopituitarism in pediatric survivors of inflicted traumatic brain injury. Journal of Neurotrauma 31(4): 321-6	- Not a prognostic study
Aylanc, H.; Tutunculer, F.; Sut, N. (2016) Evaluation of pituitary function in cases with the diagnosis of pediatric mild traumatic brain injury: Cross-sectional study. Journal of Neurosciences in Rural Practice 7(4): 537-543	- Correlation data only
Bavisetty, S., Bavisetty, S., McArthur, D. L. et al. (2008) Chronic hypopituitarism after traumatic brain injury: risk assessment and relationship to outcome. Neurosurgery 62(5): 1080-93; discussion 1093	- No multivariate analysis for outcomes relevant to the review protocol
Baxter, D., Sharp, D. J., Feeney, C. et al. (2013) Pituitary dysfunction after blast traumatic brain injury: The UK BIOSAP study. Annals of Neurology 74(4): 527-36	- No multivariate analysis for outcomes relevant to the review protocol
Bellone, S., Einaudi, S., Caputo, M. et al. (2013) Measurement of height velocity is an useful marker for monitoring pituitary function in patients who had traumatic brain injury. Pituitary 16(4): 499-506	- Correlation data only
Berg, C., Oeffner, A., Schumm-Draeger, P. M. et al. (2010) Prevalence of anterior pituitary dysfunction in patients following traumatic brain injury in a German multi-centre screening program. Experimental & Clinical Endocrinology & Diabetes 118(2): 139-44	- Not a prognostic study
Bondanelli, M., De Marinis, L., Ambrosio, M. R. et al. (2004) Occurrence of pituitary dysfunction following traumatic brain injury. Journal of Neurotrauma 21(6): 685-96	- No multivariate analysis for outcomes relevant to the review protocol
Briet, C., Braun, K., Lefranc, M. et al. (2019) Should We Assess Pituitary Function in Children After a Mild Traumatic Brain Injury? A Prospective Study. Frontiers in Endocrinology 10: 149	- Data not reported in an extractable format that can be analysed
Capatina, C., Capatina, C. O., Chirica, V. I. et al. (2016) Endocrine consequences of traumatic brain injury. Literature review. Romanian Journal of Legal Medicine 24(3): 199-203	- Review article but not a systematic review

Study	Code [Reason]
Casano-Sancho, P., Suarez, L., Ibanez, L. et al. (2013) Pituitary dysfunction after traumatic brain injury in children: is there a need for ongoing endocrine assessment?. Clinical Endocrinology 79(6): 853-8	- Not a prognostic study
Castro, A. I., Lage, M., Peino, R. et al. (2007) A single growth hormone determination 30 minutes after the administration of the GHRH plus GHRP-6 test is sufficient for the diagnosis of somatotrope dysfunction in patients who have suffered traumatic brain injury. Journal of Endocrinological Investigation 30(3): 224-9	- Not a prognostic study
Cuesta, M., Hannon, M. J., Crowley, R. K. et al. (2016) Symptoms of gonadal dysfunction are more predictive of hypopituitarism than nonspecific symptoms in screening for pituitary dysfunction following moderate or severe traumatic brain injury. Clinical Endocrinology 84(1): 92-8	- Prognostic variables assessed in chronic phase (e.g. >1 year after injury) rather than at time of injury
Dalwadi, P. P., Bhagwat, N. M., Tayde, P. S. et al. (2017) Pituitary dysfunction in traumatic brain injury: Is evaluation in the acute phase worthwhile?. Indian Journal of Endocrinology and Metabolism 21(1): 80-84	- No multivariate analysis for outcomes relevant to the review protocol - Correlation data only
Dassa, Y., Crosnier, H., Chevignard, M. et al. (2019) Pituitary deficiency and precocious puberty after childhood severe traumatic brain injury: a long-term follow-up prospective study. European Journal of Endocrinology 180(5): 281-290	- Correlation data only
Dhume, C. Y. and Demelo, M. (2012) Assessment of hormonal levels in traumatic head injury. International Journal of Pharma and Bio Sciences 3(4): 348-357	- Full text paper not available
Fernandez-Rodriguez, E., Bernabeu, I., Castro, A. I. et al. (2011) Hypopituitarism following traumatic brain injury: determining factors for diagnosis. Frontiers in Endocrinology 2: 25	- Review article but not a systematic review
Giordano, G.; Aimaretti, G.; Ghigo, E. (2005) Variations of pituitary function over time after brain injuries: the lesson from a prospective study. Pituitary 8(34): 227-31	- Not a prognostic study

Study	Code [Reason]
Giuliano, S., Talarico, S., Bruno, L. et al. (2017) Growth hormone deficiency and hypopituitarism in adults after complicated mild traumatic brain injury. Endocrine 58(1): 115-123	- Correlation data only
Glynn, N. and Agha, A. (2013) Which patient requires neuroendocrine assessment following traumatic brain injury, when and how?. Clinical Endocrinology 78(1): 17-20	- Review article but not a systematic review
Glynn, N. and Agha, A. (2019) The frequency and the diagnosis of pituitary dysfunction after traumatic brain injury. Pituitary 22(3): 249-260	- Review article but not a systematic review
Gupta, P., Mittal, R. S., Sharma, A. et al. (2021) Endocrine Dysfunction in Traumatic Subarachnoid Hemorrhage: A Prospective Study. Indian Journal of Neurosurgery.	- Correlation data only
Hacioglu, A. and Kelestemur, F. (2019) Neuroendocrine consequences of traumatic brain injury and strategies for its management. Erciyes Medical Journal 41(4): 357-363	- Review article but not a systematic review
Hacioglu, A.; Kelestimur, F.; Tanriverdi, F. (2020) Long-term neuroendocrine consequences of traumatic brain injury and strategies for management. Expert Review of Endocrinology & Metabolism 15(2): 123-139	- Review article but not a systematic review
Hannon, M. J., Crowley, R. K., Behan, L. A. et al. (2013) Acute glucocorticoid deficiency and diabetes insipidus are common after acute traumatic brain injury and predict mortality. Journal of Clinical Endocrinology & Metabolism 98(8): 3229-37	- Correlation data only
Hari Kumar, K. V.; Swamy, M. N.; Khan, M. A. (2016) Prevalence of hypothalamo pituitary dysfunction in patients of traumatic brain injury. Indian Journal of Endocrinology and Metabolism 20(6): 772-778	- No multivariate analysis for outcomes relevant to the review protocol
Herrmann, B. L., Rehder, J., Kahlke, S. et al. (2006) Hypopituitarism following severe traumatic brain injury. Experimental & Clinical Endocrinology & Diabetes 114(6): 316-21	- Correlation data only
Hwang, S. L., Lieu, A. S., Howng, S. L. et al. (1998) Hypothalamic dysfunction in acute head-	- Correlation data only

Study	Code [Reason]
injured patients with stress ulcer. Kaohsiung Journal of Medical Sciences 14(9): 554-60	
Idowu, O. E.; Obafunwa, J. O.; Soyemi, S. O. (2017) Pituitary gland trauma in fatal nonsurgical closed traumatic brain injury. Brain Injury 31(3): 359-362	- Prognostic factors not relevant to review protocol
Ioachimescu, A. G., Hampstead, B. M., Moore, A. et al. (2015) Growth hormone deficiency after mild combat-related traumatic brain injury. Pituitary 18(4): 535-41	- Not a prognostic study
Izzo, G., Tirelli, A., Angrisani, E. et al. (2016) Pituitary dysfunction and its association with quality of life in traumatic brain injury. International Journal Of Surgery 28suppl1: S103-8	- Outcomes not relevant to review protocol
Jeong, J. H., Kim, Y. Z., Cho, Y. W. et al. (2010) Negative effect of hypopituitarism following brain trauma in patients with diffuse axonal injury. Journal of Neurosurgery 113(3): 532-8	- No multivariate analysis for outcomes relevant to the review protocol
Kelestimur, F. (2009) Growth hormone deficiency after traumatic brain injury in adults: when to test and how to treat?. Pediatric Endocrinology Reviews 6suppl4: 534-9	- Review article but not a systematic review
Kelly, D. F., Chaloner, C., Evans, D. et al. (2014) Prevalence of pituitary hormone dysfunction, metabolic syndrome, and impaired quality of life in retired professional football players: a prospective study. Journal of Neurotrauma 31(13): 1161-71	- No multivariate analysis for outcomes relevant to the review protocol
Kelly, D. F., Gonzalo, I. T., Cohan, P. et al. (2000) Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. Journal of Neurosurgery 93(5): 743-52	- No multivariate analysis for outcomes relevant to the review protocol
Khadr, S. N., Crofton, P. M., Jones, P. A. et al. (2010) Evaluation of pituitary function after traumatic brain injury in childhood. Clinical Endocrinology 73(5): 637-43	- No prognostic analysis - limited to P-values for differences between groups
Khajeh, L., Blijdorp, K., Neggers, S. J. et al. (2014) Hypopituitarism after subarachnoid haemorrhage, do we know enough?. BMC neurology 14(1): 205	- Population - systematic review excluded TBI

Study	Code [Reason]
Kibayashi, K., Shimada, R., Nakao, K. et al. (2012) Analysis of pituitary lesions in fatal closed head injury. American Journal of Forensic Medicine & Pathology 33(3): 206-10	- Prognostic factors not relevant to review protocol
Kleindienst, A., Brabant, G., Bock, C. et al. (2009) Neuroendocrine function following traumatic brain injury and subsequent intensive care treatment: a prospective longitudinal evaluation. Journal of Neurotrauma 26(9): 1435-46	- Correlation data only
Klose, M. and Feldt-Rasmussen, U. (2008) Does the type and severity of brain injury predict hypothalamo-pituitary dysfunction? Does post-traumatic hypopituitarism predict worse outcome?. Pituitary 11(3): 255-61	- Review article but not a systematic review
Klose, M., Juul, A., Struck, J. et al. (2007) Acute and long-term pituitary insufficiency in traumatic brain injury: a prospective single-centre study. Clinical Endocrinology 67(4): 598-606	- No multivariate analysis for outcomes relevant to the review protocol
Klose, M., Stochholm, K., Janukonyte, J. et al. (2015) Patient reported outcome in posttraumatic pituitary deficiency: results from The Danish National Study on posttraumatic hypopituitarism. European Journal of Endocrinology 172(6): 753-62	- No multivariate analysis for outcomes relevant to the review protocol
Klose, M., Stochholm, K., Janukonyte, J. et al. (2014) Prevalence of posttraumatic growth hormone deficiency is highly dependent on the diagnostic set-up: results from The Danish National Study on Posttraumatic Hypopituitarism. Journal of Clinical Endocrinology & Metabolism 99(1): 101-10	- No multivariate analysis for outcomes relevant to the review protocol
Klose, M., Watt, T., Brennum, J. et al. (2007) Posttraumatic hypopituitarism is associated with an unfavorable body composition and lipid profile, and decreased quality of life 12 months after injury. Journal of Clinical Endocrinology & Metabolism 92(10): 3861-8	- Data not reported in an extractable format that can be analysed
Kokshoorn, N. E., Smit, J. W., Nieuwlaat, W. A. et al. (2011) Low prevalence of hypopituitarism after traumatic brain injury: a multicenter study. European Journal of Endocrinology 165(2): 225-31	- Outcomes not relevant to review protocol - Data not reported in an extractable format that can be analysed

Study	Code [Reason]
Kokshoorn, N. E., Wassenaar, M. J., Biermasz, N. R. et al. (2010) Hypopituitarism following traumatic brain injury: prevalence is affected by the use of different dynamic tests and different normal values. European Journal of Endocrinology 162(1): 11-8	- Systematic review used as source of primary studies
Kopczak, A., Kilimann, I., von Rosen, F. et al. (2014) Screening for hypopituitarism in 509 patients with traumatic brain injury or subarachnoid hemorrhage. Journal of Neurotrauma 31(1): 99-107	- Prognostic factors not relevant to review protocol
Kozlowski Moreau, O., Yollin, E., Merlen, E. et al. (2012) Lasting pituitary hormone deficiency after traumatic brain injury. Journal of Neurotrauma 29(1): 81-9	- No multivariate analysis for outcomes relevant to the review protocol
Krahulik, D., Aleksijevic, D., Smolka, V. et al. (2017) Prospective study of hypothalamo-hypophyseal dysfunction in children and adolescents following traumatic brain injury. Biomedical Papers of the Medical Faculty of Palacky University in Olomouc, Czech Republic 161(1): 80-85	- No multivariate analysis for outcomes relevant to the review protocol
Krahulik, D., Zapletalova, J., Frysak, Z. et al. (2010) Dysfunction of hypothalamic-hypophysial axis after traumatic brain injury in adults. Journal of Neurosurgery 113(3): 581-4	- No multivariate analysis for outcomes relevant to the review protocol
Kreber, L. A.; Griesbach, G. S.; Ashley, M. J. (2016) Detection of Growth Hormone Deficiency in Adults with Chronic Traumatic Brain Injury. Journal of Neurotrauma 33(17): 1607-13	- Not a prognostic study
Krewer, C., Schneider, M., Schneider, H. J. et al. (2016) Neuroendocrine Disturbances One to Five or More Years after Traumatic Brain Injury and Aneurysmal Subarachnoid Hemorrhage: Data from the German Database on Hypopituitarism. Journal of Neurotrauma 33(16): 1544-53	- Correlation data only
Lauzier, F., Turgeon, A. F., Boutin, A. et al. (2014) Clinical outcomes, predictors, and prevalence of anterior pituitary disorders following traumatic brain injury: a systematic review. Critical care medicine 42(3): 712-21	- Systematic review used as source of primary studies

Study	Code [Reason]
Leal-Cerro, A., Flores, J. M., Rincon, M. et al. (2005) Prevalence of hypopituitarism and growth hormone deficiency in adults long-term after severe traumatic brain injury. Clinical Endocrinology 62(5): 525-32	- Population - study excluded those that had no symptoms of pituitary hormone deficiency
Lee, J., Anderson, L. J., Migula, D. et al. (2021) Experience of a Pituitary Clinic for US Military Veterans With Traumatic Brain Injury. Journal of the Endocrine Society 5(4): bvab005	- Data not reported in an extractable format that can be analysed
Lee, S. C.; Zasler, N. D.; Kreutzer, J. S. (1994) Male pituitary-gonadal dysfunction following severe traumatic brain injury. Brain Injury 8(6): 571-7	- Correlation data only
Lieberman, S. A., Oberoi, A. L., Gilkison, C. R. et al. (2001) Prevalence of neuroendocrine dysfunction in patients recovering from traumatic brain injury. Journal of Clinical Endocrinology & Metabolism 86(6): 2752-6	- Correlation data only
Lithgow, K., Chin, A., Debert, C. T. et al. (2018) Utility of serum IGF-1 for diagnosis of growth hormone deficiency following traumatic brain injury and sport-related concussion. BMC Endocrine Disorders 18(1): 20	- No multivariate analysis for outcomes relevant to the review protocol
Loggini, A., Tangonan, R., El Ammar, F. et al. (2021) Neuroendocrine Dysfunction in the Acute Setting of Penetrating Brain Injury: A Systematic Review. World Neurosurgery 147: 172-180.e1	- Systematic review used as source of primary studies
Lorenzo, M., Peino, R., Castro, A. I. et al. (2005) Hypopituitarism and growth hormone deficiency in adult subjects after traumatic brain injury: who and when to test. Pituitary 8(34): 233-7	- Review article but not a systematic review
Maiya, B., Newcombe, V., Nortje, J. et al. (2008) Magnetic resonance imaging changes in the pituitary gland following acute traumatic brain injury. Intensive Care Medicine 34(3): 468-75	- Correlation data only
Malekpour, B., Mehrafshan, A., Saki, F. et al. (2012) Effect of posttraumatic serum thyroid hormone levels on severity and mortality of patients with severe traumatic brain injury. Acta Medica Iranica 50(2): 113-6	- Correlation data only
Marina, D., Klose, M., Nordenbo, A. et al. (2015) Early endocrine alterations reflect prolonged	- Outcomes not relevant to review protocol

Study	Code [Reason]
stress and relate to 1-year functional outcome in patients with severe brain injury. European Journal of Endocrinology 172(6): 813-22	
Masarsky, C. S. (2018) Hypoxic stress: A risk factor for post-concussive hypopituitarism?. Medical Hypotheses 121: 31-34	- Review article but not a systematic review
Medic-Stojanoska, M. (2009) Traumatic brain injury induced hypopituitarism in children and adolescents. Pediatric Health 3(3): 283-291	- Review article but not a systematic review
Mercier, L. J., Kruger, N., Le, Q. B. et al. (2021) Growth hormone deficiency testing and treatment following mild traumatic brain injury. Scientific Reports 11(1): 8534	- No multivariate analysis for outcomes relevant to the review protocol
Moon, R. J., Sutton, T., Wilson, P. M. et al. (2010) Pituitary function at long-term follow-up of childhood traumatic brain injury. Journal of Neurotrauma 27(10): 1827-35	- Outcomes not relevant to review protocol - Correlation data only
Moro, N., Katayama, Y., Igarashi, T. et al. (2007) Hyponatremia in patients with traumatic brain injury: incidence, mechanism, and response to sodium supplementation or retention therapy with hydrocortisone. Surgical Neurology 68(4): 387-93	- Outcomes not relevant to review protocol
Nemes, O., Kovacs, N., Czeiter, E. et al. (2015) Predictors of post-traumatic pituitary failure during long-term follow-up. Hormones 14(3): 383-91	- Data not reported in an extractable format that can be analysed
Nemes, O., Kovacs, N., Szujo, S. et al. (2016) Can early clinical parameters predict post-traumatic pituitary dysfunction in severe traumatic brain injury?. Acta Neurochirurgica 158(12): 2347-2353	- No multivariate analysis for outcomes relevant to the review protocol
Niederland, T., Makovi, H., Gal, V. et al. (2007) Abnormalities of pituitary function after traumatic brain injury in children. Journal of Neurotrauma 24(1): 119-27	- Not a prognostic study
Nordon, D. G., Guimaraes, R. R., Nigri, A. A. et al. (2012) Mild traumatic brain injury and immediate hypopituitarism in children. Scientia Medica 22(2): 86-90	- No multivariate analysis for outcomes relevant to the review protocol

Study	Code [Reason]
Norwood, K. W., Deboer, M. D., Gurka, M. J. et al. (2010) Traumatic brain injury in children and adolescents: surveillance for pituitary dysfunction. Clinical Pediatrics 49(11): 1044-9	- No multivariate analysis for outcomes relevant to the review protocol
Ntali, G. and Tsagarakis, S. (2020) Pituitary dysfunction after traumatic brain injury: prevalence and screening strategies. Expert Review of Endocrinology & Metabolism 15(5): 341-354	- Review article but not a systematic review
Ntali, G. and Tsagarakis, S. (2019) Traumatic brain injury induced neuroendocrine changes: acute hormonal changes of anterior pituitary function. Pituitary 22(3): 283-295	- Review article but not a systematic review
Obiols Alfonso, G. (2012) Impact of head trauma on pituitary function. Endocrinologia y Nutricion 59(8): 505-15	- Study not reported in English
Park, K. D., Kim, D. Y., Lee, J. K. et al. (2010) Anterior pituitary dysfunction in moderate-to-severe chronic traumatic brain injury patients and the influence on functional outcome. Brain Injury 24(11): 1330-5	- No multivariate analysis for outcomes relevant to the review protocol
Pavlovic, D., Pekic, S., Stojanovic, M. et al. (2010) Chronic cognitive sequelae after traumatic brain injury are not related to growth hormone deficiency in adults. European Journal of Neurology 17(5): 696-702	- No multivariate analysis for outcomes relevant to the review protocol
Pekic, S. and Popovic, V. (2017) DIAGNOSIS OF ENDOCRINE DISEASE: Expanding the cause of hypopituitarism. European Journal of Endocrinology 176(6): R269-R282	- Review article but not a systematic review
Personnier, C., Crosnier, H., Meyer, P. et al. (2014) Prevalence of pituitary dysfunction after severe traumatic brain injury in children and adolescents: a large prospective study. Journal of Clinical Endocrinology & Metabolism 99(6): 2052-60	- No multivariate analysis for outcomes relevant to the review protocol
Popovic, V., Pekic, S., Pavlovic, D. et al. (2004) Hypopituitarism as a consequence of traumatic brain injury (TBI) and its possible relation with cognitive disabilities and mental distress. Journal of Endocrinological Investigation 27(11): 1048-54	- No multivariate analysis for outcomes relevant to the review protocol

Study	Code [Reason]
Porto, L., Margerkurth, J., Althaus, J. et al. (2011) Morphometry of the pituitary gland and hypothalamus in long-term survivors of childhood trauma. Childs Nervous System 27(11): 1937-41	- Not a prognostic study
Powner, D. J., Boccalandro, C., Alp, M. S. et al. (2006) Endocrine failure after traumatic brain injury in adults. Neurocritical Care 5(1): 61-70	- Review article but not a systematic review
Prasanna, K. L.; Mittal, R. S.; Gandhi, A. (2015) Neuroendocrine dysfunction in acute phase of moderate-to-severe traumatic brain injury: a prospective study. Brain Injury 29(3): 336-42	- Correlation data only
Prodam, F., Gasco, V., Caputo, M. et al. (2013) Metabolic alterations in patients who develop traumatic brain injury (TBI)-induced hypopituitarism. Growth Hormone & Igf Research 23(4): 109-13	- Prognostic variables assessed in chronic phase (e.g. >1 year after injury) rather than at time of injury
Rabelink, N. M., Peeters, G. M., van Schoor, N. M. et al. (2011) Self-reported loss of consciousness after head trauma does not predispose to hypopituitarism in an older population. Journal of Head Trauma Rehabilitation 26(1): 90-7	- Population - self-reported head injury with loss of consciousness only, therefore unreliable
Reifschneider, K.; Auble, B. A.; Rose, S. R. (2015) Update of Endocrine Dysfunction following Pediatric Traumatic Brain Injury. Journal of Clinical Medicine 4(8): 1536-60	- Review article but not a systematic review
Renner, C., Hummelsheim, H., Kopczak, A. et al. (2012) The influence of gender on the injury severity, course and outcome of traumatic brain injury. Brain Injury 26(11): 1360-71	- Data not reported in an extractable format that can be analysed
Salomon-Estebanez, M. A., Grau, G., Vela, A. et al. (2014) Is routine endocrine evaluation necessary after paediatric traumatic brain injury?. Journal of Endocrinological Investigation 37(2): 143-8	- Not a prognostic study
Samadani, U.; Reyes-Moreno, I.; Buchfelder, M. (2005) Endocrine dysfunction following traumatic brain injury: mechanisms, pathophysiology and clinical correlations. Acta Neurochirurgica - Supplement 93: 121-5	- Review article but not a systematic review

Study	Code [Reason]
Sav, A., Rotondo, F., Syro, L. V. et al. (2019) Pituitary pathology in traumatic brain injury: a review. Pituitary 22(3): 201-211	- Review article but not a systematic review
Schneider, H. J., Corneli, G., Kreitschman-Andermahr, I. et al. (2007) Traumatic brain injury and hypopituitarism in children and adolescents: is the problem under-estimated?. Pediatric Endocrinology Reviews 4(3): 205-9	- Review article but not a systematic review
Schneider, H. J., Kreitschmann-Andermahr, I., Ghigo, E. et al. (2007) Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a systematic review. JAMA 298(12): 1429-38	- Systematic review used as source of primary studies
Schneider, H. J., Samann, P. G., Schneider, M. et al. (2007) Pituitary imaging abnormalities in patients with and without hypopituitarism after traumatic brain injury. Journal of Endocrinological Investigation 30(4): RC9-RC12	- No multivariate analysis for outcomes relevant to the review protocol
Schneider, H. J., Schneider, M., Kreitschmann-Andermahr, I. et al. (2011) Structured assessment of hypopituitarism after traumatic brain injury and aneurysmal subarachnoid hemorrhage in 1242 patients: the German interdisciplinary database. Journal of Neurotrauma 28(9): 1693-8	- No prognostic analysis - limited to P-values for differences between groups
Schneider, H. J., Schneider, M., Saller, B. et al. (2006) Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. European Journal of Endocrinology 154(2): 259-65	- No multivariate analysis for outcomes relevant to the review protocol
Schneider, M., Schneider, H. J., Yassouridis, A. et al. (2008) Predictors of anterior pituitary insufficiency after traumatic brain injury. Clinical Endocrinology 68(2): 206-12	- Data not reported in an extractable format that can be analysed
Silva, P. P., Bhatnagar, S., Herman, S. D. et al. (2015) Predictors of Hypopituitarism in Patients with Traumatic Brain Injury. Journal of Neurotrauma 32(22): 1789-95	- No multivariate analysis for outcomes relevant to the review protocol
Soliman, A. T., Adel, A., Soliman, N. A. et al. (2015) Pituitary Deficiency Following Traumatic Brain Injury in Early Childhood: A Review of the Literature. Georgian Medical News: 62-71	- Review article but not a systematic review

Study	Code [Reason]
Su, D. H.; Chang, Y. C.; Chang, C. C. (2005) Post-traumatic anterior and posterior pituitary dysfunction. Journal of the Formosan Medical Association 104(7): 463-7	- Population - only included those with confirmed history of hypopituitarism - Not a prognostic study
Tan, C. L., Alavi, S. A., Baldeweg, S. E. et al. (2017) The screening and management of pituitary dysfunction following traumatic brain injury in adults: British Neurotrauma Group guidance. Journal of Neurology, Neurosurgery & Psychiatry 88(11): 971-981	- Systematic review used as source of primary studies
Tan, C. L. and Hutchinson, P. J. (2019) A neurosurgical approach to traumatic brain injury and post-traumatic hypopituitarism. Pituitary 22(3): 332-337	- Systematic review used as source of primary studies
Tanriverdi, F., De Bellis, A., Ulutabanca, H. et al. (2013) A five year prospective investigation of anterior pituitary function after traumatic brain injury: is hypopituitarism long-term after head trauma associated with autoimmunity?. Journal of Neurotrauma 30(16): 1426-33	- No prognostic analysis - limited to P-values for differences between groups
Tanriverdi, F., Senyurek, H., Unluhizarci, K. et al. (2006) High risk of hypopituitarism after traumatic brain injury: a prospective investigation of anterior pituitary function in the acute phase and 12 months after trauma. Journal of Clinical Endocrinology & Metabolism 91(6): 2105-11	- No multivariate analysis for outcomes relevant to the review protocol
Tanriverdi, F., Taheri, S., Ulutabanca, H. et al. (2008) Apolipoprotein E3/E3 genotype decreases the risk of pituitary dysfunction after traumatic brain injury due to various causes: preliminary data. Journal of Neurotrauma 25(9): 1071-7	- Prognostic factors not relevant to review protocol - No multivariate analysis for outcomes relevant to the review protocol
Tanriverdi, F., Ulutabanca, H., Unluhizarci, K. et al. (2008) Three years prospective investigation of anterior pituitary function after traumatic brain injury: a pilot study. Clinical Endocrinology 68(4): 573-9	- Not a prognostic study
Tanriverdi, F., Ulutabanca, H., Unluhizarci, K. et al. (2007) Pituitary functions in the acute phase of traumatic brain injury: are they related to severity of the injury or mortality?. Brain Injury 21(4): 433-9	- Correlation data only

Study	Code [Reason]
Tanriverdi, F.; Unluhizarci, K.; Kelestimur, F. (2010) Pituitary function in subjects with mild traumatic brain injury: a review of literature and proposal of a screening strategy. Pituitary 13(2): 146-53	- Systematic review used as source of primary studies
Tolli, A., Borg, J., Bellander, B. M. et al. (2017) Pituitary function within the first year after traumatic brain injury or subarachnoid haemorrhage. Journal of Endocrinological Investigation 40(2): 193-205	- No multivariate analysis for outcomes relevant to the review protocol
Tritos, N. A., Yuen, K. C., Kelly, D. F. et al. (2015) American Association of Clinical Endocrinologists and American College of Endocrinology Disease State Clinical Review: A Neuroendocrine Approach to Patients with Traumatic Brain Injury. Endocrine Practice 21(7): 823-31	- Review article but not a systematic review
Ulfarsson, T., Arnar Gudnason, G., Rosen, T. et al. (2013) Pituitary function and functional outcome in adults after severe traumatic brain injury: the long-term perspective. Journal of Neurotrauma 30(4): 271-80	- No multivariate analysis for outcomes relevant to the review protocol
Ulutabanca, H., Hatipoglu, N., Karaca, Z. et al. (2013) Evaluation of TSH and ACTH hormone levels during the acute phase after traumatic brain injury in pediatric cases. Erciyes Tip Dergisi 35(3): 128-131	- Study not reported in English
Ulutabanca, H., Hatipoglu, N., Tanriverdi, F. et al. (2014) Prospective investigation of anterior pituitary function in the acute phase and 12 months after pediatric traumatic brain injury. Childs Nervous System 30(6): 1021-8	- Correlation data only
Undurti, A., Colasurdo, E. A., Sikkema, C. L. et al. (2018) Chronic Hypopituitarism Associated with Increased Postconcussive Symptoms Is Prevalent after Blast-Induced Mild Traumatic Brain Injury. Frontiers in neurology [electronic resource]. 9: 72	- Data not reported in an extractable format that can be analysed
Urban, R. J.; Harris, P.; Masel, B. (2005) Anterior hypopituitarism following traumatic brain injury. Brain Injury 19(5): 349-58	- Review article but not a systematic review
van der Eerden, A. W., Twickler, M. T., Sweep, F. C. et al. (2010) Should anterior pituitary	- Not a prognostic study

Study	Code [Reason]
function be tested during follow-up of all patients presenting at the emergency department because of traumatic brain injury?. European Journal of Endocrinology 162(1): 19-28	
Wachter, D., Gundling, K., Oertel, M. F. et al. (2009) Pituitary insufficiency after traumatic brain injury. Journal of Clinical Neuroscience 16(2): 202-8	- No multivariate analysis for outcomes relevant to the review protocol
Wagner, J., Dusick, J. R., McArthur, D. L. et al. (2010) Acute gonadotroph and somatotroph hormonal suppression after traumatic brain injury. Journal of Neurotrauma 27(6): 1007-19	- Data not reported in an extractable format that can be analysed
West, A. N.; Diaz-Thomas, A. M.; Shafi, N. I. (2020) Evidence Limitations in Determining Sexually Dimorphic Outcomes in Pediatric Post-Traumatic Hypopituitarism and the Path Forward. Frontiers in neurology [electronic resource]. 11: 551923	- Review article but not a systematic review
Zheng, P., He, B., Guo, Y. et al. (2015) Decreased apparent diffusion coefficient in the pituitary and correlation with hypopituitarism in patients with traumatic brain injury. Journal of Neurosurgery 123(1): 75-80	- No multivariate analysis for outcomes relevant to the review protocol
Zheng, P.; He, B.; Tong, W. (2014) Dynamic pituitary hormones change after traumatic brain injury. Neurology India 62(3): 280-4	- No multivariate analysis for outcomes relevant to the review protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.