National Institute for Health and Care Excellence

Final

Head Injury: assessment and early management

[N] Evidence reviews for identification of hypopituitarism (when to investigate)

NICE guideline NG232

Evidence reviews underpinning recommendations 1.9.6 to 1.9.8 and 1.10.13 to 1.10.15 a research recommendation in the NICE guideline

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Final

Developed by National Institute for Health and Care Excellence

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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1.1 Review question

When should people with head injury be investigated for hypopituitarism?

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 when people with head injury should be investigated for hypopituitarism.

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 who are being screened for hypopituitarism: • 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 and stratify by Glasgow Coma Scale (GCS) severity: • Mild GCS score 13-15 • Moderate GCS score 9-12 • Severe GCS score 3-8

	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.
Intervention	Investigation for hypopituitarism in acute phase Strata: 1. In ED 2. Admission in hospital but not in ED 3. After discharge, within 1 year of injury *All timepoints are relevant for investigations for hypopituitarism* *Note from studies if the investigation was ad-hoc or if it was routine screening.* *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.*
Comparison	Investigation for hypopituitarism in chronic phase: • ≥1 year after injury
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality • Quality of life (all validated quality of life scores). • Need for treatment of hypopituitarism (growth rate for children will be covered here) • Time to treatment of hypopituitarism • Return to work/return to school Same outcomes applicable to both adults and children. All-follow-up times will be considered.
Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders, starting with prospective cohort studies. Key confounders: *Adults:* • Extent of extra cranial injury (other organ support) *Children:* • Extent of extra cranial injury (other organ support) • Age (in children- young child not in adults) Note from committee: If there are insufficient studies (quantity and/or quality) found that adjust for key confounders, studies that do not adjust for these confounders will be included. Studies will be downgraded for indirectness if not adjusted for key confounders.

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 Effectiveness evidence

1.1.4.1 Included studies

Searches were performed for both randomised controlled trials and observational studies matching the protocol, as well as systematic reviews of these types of studies, which compared at least two different groups of people with differing time-points for investigation of hypopituitarism (acute vs. chronic). However, no relevant studies comparing relevant outcomes between two groups of people were identified. Various studies did compare the prevalence of hypopituitarism at different time-points in the same group of people, but these did not match the review protocol as repeated testing in the same group of people does not give insight into whether timing of testing affects clinical outcomes, such as mortality or quality of life specified in the protocol, which was the aim of this review protocol.

See also the study selection flow chart in Appendix C.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

No clinical evidence was identified for this review.

1.1.6 Summary of the effectiveness evidence

No clinical evidence was identified for this review.

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

Modelling was not conducted for this review.

1.1.10 Evidence statements

Effectiveness/Qualitative

- No clinical evidence was identified for this review.

Economic

- No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes that matter most

The committee considered all outcomes as equally important for decision making and therefore have all been rated as critical: mortality, quality of life, need for treatment of hypopituitarism (including growth rate of children), time to treatment of hypopituitarism and return to work/return to school). All outcomes related to adults and children. All follow-up times were considered, as the committee acknowledged that studies with a long duration of follow-up can be difficult to conduct.

No studies suitable for this review were identified, as there were no studies comparing two different groups of people with differing time-points for investigation of hypopituitarism (acute vs. chronic). There were studies that compared the prevalence of hypopituitarism at different time points in the same group of people but this did not match the protocol.

1.1.11.2 The quality of the evidence

No clinical evidence was included in this review.

1.1.11.3 Benefits and harms

No evidence was included in this review. The committee acknowledged that hypopituitarism can be difficult to recognise early on which can lead to delay in diagnosis and treatment. They therefore thought it important to make a research recommendation to identify those who may have hypopituitarism. The committee based the research recommendation on the original review question to discover the best time to investigate those with head injury for hypopituitarism. This would include finding out the incidence of hypopituitarism in head injury. The committee thought that finding out the rates of hypopituitarism after head injury in different cohorts (intensive care, admitted to wards, people discharged) would be useful, and how it depends on the time it is measured in future research.

1.1.11.4 Cost effectiveness and resource use

No economic evaluations were found for this question. Given the lack of both clinical and economic evidence the committee decided to make a research recommendation.

1.1.11.5 Other factors the committee took into account

None.

References

1. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction

Appendices

Appendix A – Review protocols

Review protocol for identification of hypopituitarism (when to investigate)

ID	Field	Content
0.	PROSPERO registration number	CRD42022327402
1.	Review title	When should people with head injury be investigated for hypopituitarism? TBI may cause pituitary gland dysfunction contributing to significant morbidity and mortality from TBI. Inadequate secretion of one or more of the hormones secreted by the pituitary is known as hypopituitarism. Hormones secreted by pituitary gland: ACTCH (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 Current practice when are they investigated? Not everyone gets investigated. People are investigated when they are symptomatic.
2.	Review question	When should people with head injury be investigated for hypopituitarism?
3.	Objective	To determine when should people with head injury be investigated for hypopituitarism. There is currently no guidance for the screening and detection of hypopituitarism patients with TBI, with significant variation in practice. Scope comments: As hypopituitarism symptoms may not be immediate, importance of advising of follow up visit to GP with related head injury/pituitary symptoms, and recording this clearly on medical records. Discharge and follow up- may not be possible to identify hypopituitarism if discharge is within shorter time frame i.e few days/weeks. Hypopituitarism symptoms may not manifest immediately.
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 head injury who are being screened for hypopituitarism • 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 score 13-15 • Moderate GCS score 9-12 • Severe GCS score 3-8 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.	Intervention	Investigation for hypopituitarism in acute phase Strata: 1. In ED 2. Admission in hospital but not in ED 3. After discharge, within 1 year of injury All timepoints are relevant for investigations for hypopituitarism Note from studies if the investigation was adhoc or if it was routine screening. 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.
8.	Comparator	Investigation for hypopituitarism in chronic phase ➢ ≥1 year after injury
9.	Types of study to be included	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no RCT evidence is available, non-randomised studies will be considered if they adjust for key confounders, starting with prospective cohort studies. Key confounders: Adults: • Extent of extra cranial injury (other organ support) Children: • Extent of extra cranial injury (other organ support) • Age (in children- young child not in adults) Note from committee: If there are insufficient studies (quantity and/or quality) found that adjust for key confounders, studies that do not adjust for these confounders will be included. Studies will be downgraded for indirectness if not adjusted for key confounders.
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
11.	Context	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)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality • Quality of life(all validated quality of life scores). • Need for treatment of hypopituitarism (growth rate for children will be covered here) • Time to treatment of hypopituitarism • Return to work/return to school Same outcomes applicable to both adults and children. All-follow-up times will be considered.
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	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	• Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.

		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. • GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. 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/ • Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: None identified	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative

		☐	Epidemiologic	
		☐	Service Delivery	
		☐	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date			
21.	Anticipated completion date			
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☑
		Piloting of the study selection process	☐	☑
		Formal screening of search results against eligibility criteria	☐	☑
		Data extraction	☐	☑
		Risk of bias (quality) assessment	☐	☑
		Data analysis	☐	☑
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail		

		headinjury@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)
24.	Review team members	From the National Guideline Centre: Guideline lead: Sharon Swain Senior systematic reviewer: Sharangini Rajesh Senior systematic reviewer: Julie Neilson Health economist: David Wonderling Information specialist: Joseph Runicles Project manager: Giulia Zuodar
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: 1 (nice.org.uk) .	
28.	Other registration details		
29.	Reference/URL for published protocol		
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	hypopituitarism	
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		
35.	Details of final publication	www.nice.org.uk	

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).[1] **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.

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.[1]

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 2: 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

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

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

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 3: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 22 June 2022 Quality of Life 1946 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 22 June 2022 Quality of Life 1974 – 22 June 2022	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception – 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)

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)

NHS EED and HTA (CRD) search terms

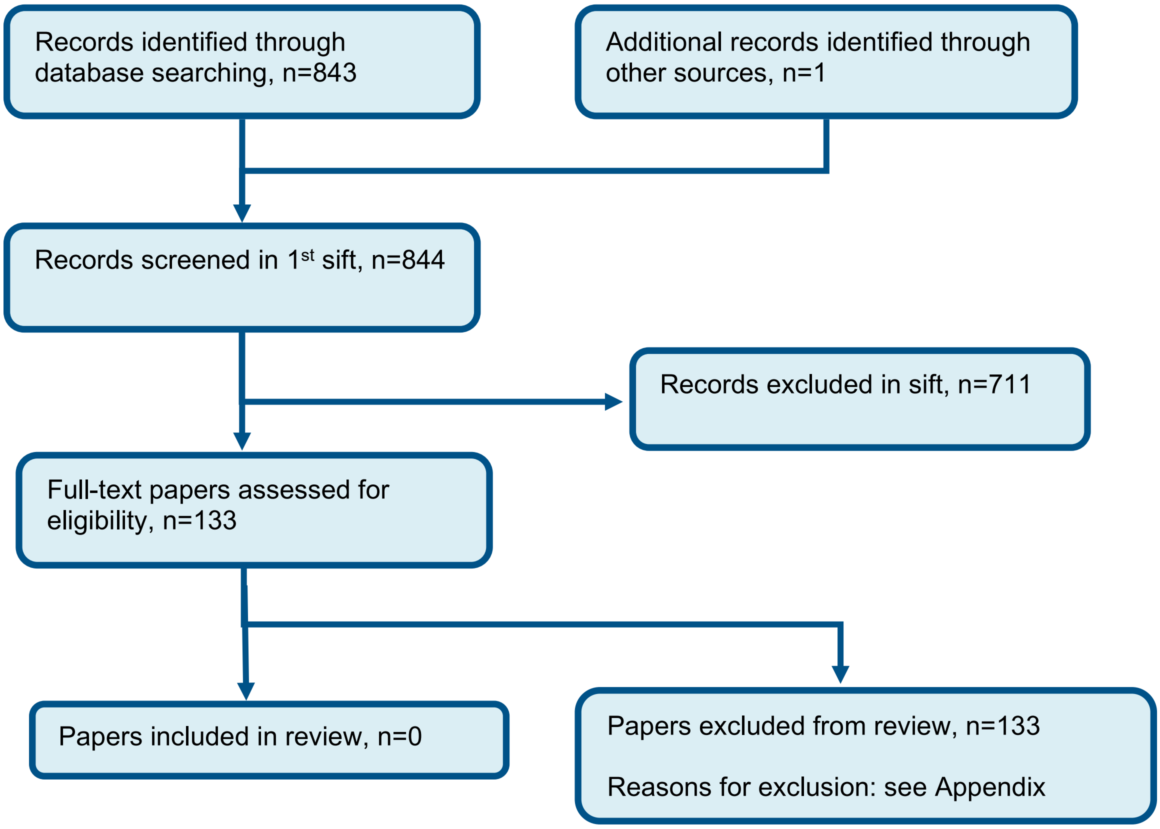
#1.	MeSH DESCRIPTOR Brain Injuries EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Craniocerebral Trauma
#3.	MeSH DESCRIPTOR Coma, Post-Head Injury
#4.	MeSH DESCRIPTOR Head Injuries, Closed EXPLODE ALL TREES
#5.	MeSH DESCRIPTOR Head Injuries, Penetrating
#6.	MeSH DESCRIPTOR Intracranial Hemorrhage, Traumatic EXPLODE 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

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])

Appendix C – Effectiveness evidence study selection

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



Appendix D – Effectiveness evidence

No clinical evidence was identified for this review.

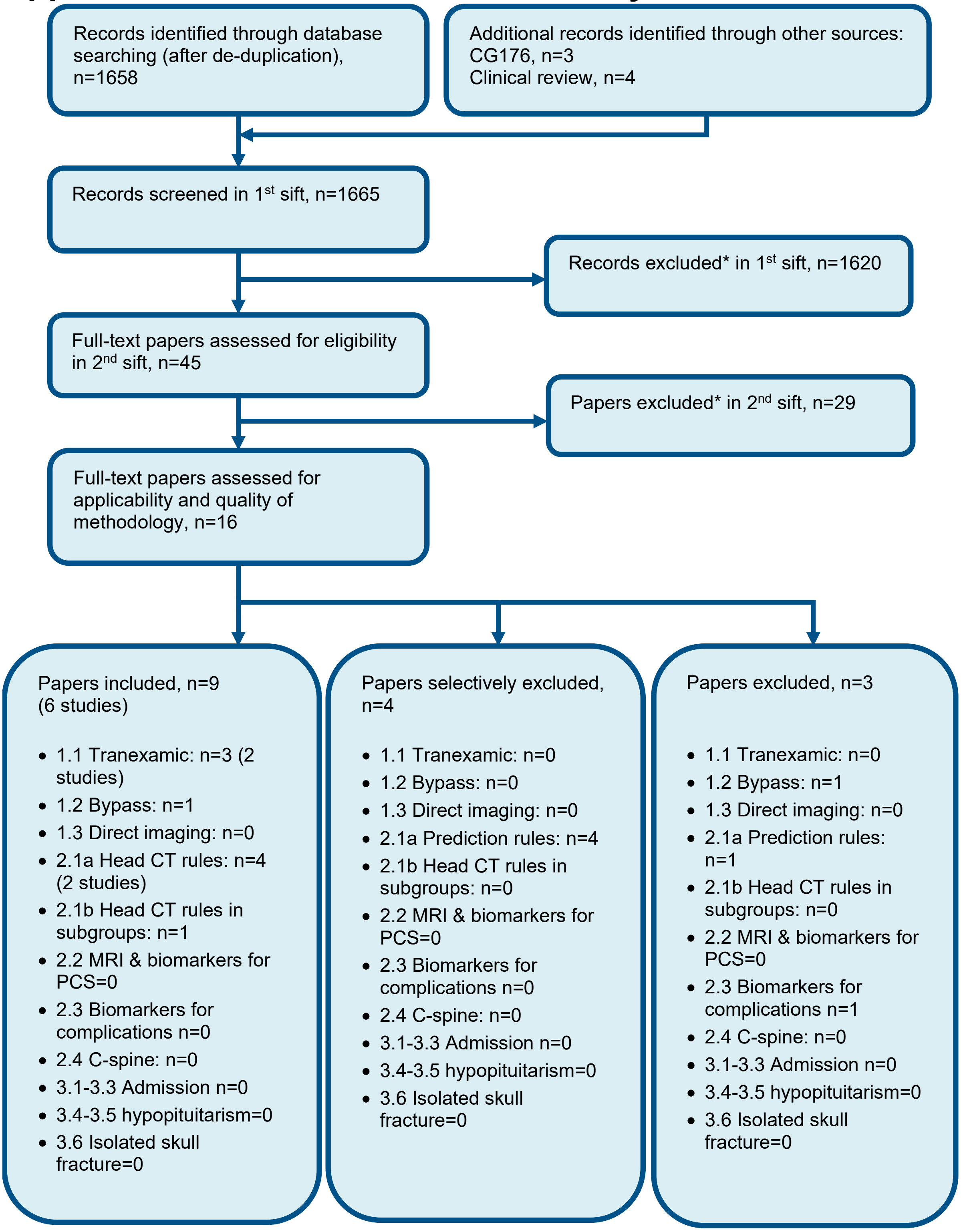
Appendix E – Forest plots

No clinical evidence was identified for this review.

Appendix F – GRADE and/or GRADE-CERQual tables

No clinical evidence was identified for this review.

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

Modelling was not undertaken for this review.

Appendix J – Excluded studies

Clinical studies

Table 3: 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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase

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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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
Dupuis, C., Thomas, S., Faure, P. et al. (2010) Secondary adrenal insufficiency in the acute phase of pediatric traumatic brain injury. Intensive Care Medicine 36(11): 1906-13	- No comparison between two separate groups of people tested in acute vs. chronic phase
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

Study	Code [Reason]
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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.	- No comparison between two separate groups of people tested in acute vs. chronic phase
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
Hadjizacharia P, Beale EO, Inaba K et al. (2008) Acute diabetes insipidus in severe head injury: a prospective study. Journal of the American College of Surgeons 207(4): 477-484	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
Hari Kumar, K. V.; Swamy, M. N.; Khan, M. A. (2016) Prevalence of hypothalamo pituitary dysfunction in patients of traumatic brain injury.	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
Indian Journal of Endocrinology and Metabolism 20(6): 772-778	
Herrmann, B. L., Rehder, J., Kahlke, S. et al. (2006) Hypopituitarism following severe traumatic brain injury. Experimental & Clinical Endocrinology & Diabetes 114(6): 316-21	- No comparison between two separate groups of people tested in acute vs. chronic phase
Hwang, S. L., Lieu, A. S., Howng, S. L. et al. (1998) Hypothalamic dysfunction in acute head-injured patients with stress ulcer. Kaohsiung Journal of Medical Sciences 14(9): 554-60	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
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 comparison between two separate groups of people tested in acute vs. chronic phase
Khajeh, L., Blijdorp, K., Neggers, S. J. et al. (2014) Hypopituitarism after subarachnoid haemorrhage, do we know enough?. BMC neurology 14(1): 205	- Population - excludes traumatic brain injury
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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., Poulsgaard, L. et al. (2007) Prevalence and predictive factors of post-traumatic hypopituitarism. Clinical Endocrinology 67(2): 193-201	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
Hypopituitarism. Journal of Clinical Endocrinology & Metabolism 99(1): 101-10	
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- Compares people assessed at different time-points but outcomes 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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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

Study	Code [Reason]
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
Marina, D., Klose, M., Nordenbo, A. et al. (2015) Early endocrine alterations reflect prolonged stress and relate to 1-year functional outcome in patients with severe brain injury. European Journal of Endocrinology 172(6): 813-22	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase - Focus on hyponatremia not hypopituitarism
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
Nemes, O., Kovacs, N., Szujo, S. et al. (2016) Can early clinical parameters predict post-traumatic pituitary dysfunction in severe	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
traumatic brain injury?. Acta Neurochirurgica 158(12): 2347-2353	
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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

Study	Code [Reason]
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase - Population - includes based on self-reported head injury and loss of conciousness which is 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	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
severity, course and outcome of traumatic brain injury. Brain Injury 26(11): 1360-71	
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- Compares people assessed at different time-points but outcomes not relevant to review protocol - No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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:	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
preliminary data. Journal of Neurotrauma 25(9): 1071-7	
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase
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	- No comparison between two separate groups of people tested in acute vs. chronic phase
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
Yang, W. H., Chen, P. C., Wang, T. C. et al. (2016) Endocrine dysfunction following traumatic brain injury: a 5-year follow-up nationwide-based study. Scientific Reports 6: 32987	- No comparison between two separate groups of people tested in acute vs. chronic phase
You, W., Zhu, Y., Wen, L. et al. (2019) Risk Factors for Anterior Hypopituitarism in Patients With Traumatic Brain Injury. Journal of Craniofacial Surgery 30(7): 2119-2123	- No comparison between two separate groups of people tested in acute vs. chronic phase
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 comparison between two separate groups of people tested in acute vs. chronic phase

Study	Code [Reason]
Zheng, P.; He, B.; Tong, W. (2014) Dynamic pituitary hormones change after traumatic brain injury. Neurology India 62(3): 280-4	- No comparison between two separate groups of people tested in acute vs. chronic phase

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.

Appendix K – Research recommendations – full details

K.1 Research recommendation

When should people with head injury be investigated for hypopituitarism?

K.1.1 Why this is important

At present, lack of data means that a proportion of people who have traumatic brain injury are not diagnosed with endocrinopathy/hypopituitarism arising from the initial injury. Presenting symptoms are insidious in onset and not readily recognised by medical practitioners, leading to delayed or missed diagnoses and therefore suboptimal treatment. In turn, this may increase the burden of morbidity and reduce health related quality of life. Research to identify early and accurate endocrinopathy will lead to improved discharge procedures from the hospital, suitable follow up arrangements and enhanced patient satisfaction.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Research to identify early and accurate endocrinopathy will lead to improved discharge procedures from the hospital, suitable follow up arrangements and enhanced patient satisfaction.
Relevance to NICE guidance	Understanding the natural history of traumatic brain injury will be crucial to the planning of pathways of care. This will enable the development of NICE guidance that will identify people who are likely to require endocrine follow up, estimate the risk and timing of hypopituitarism and provide advice to medical practitioners and people with traumatic brain injury to optimise outcomes of care.
Relevance to the NHS	Future NICE guidance in traumatic brain injury will prioritise people for admission and discharge and therefore positively impact on patient flow, encourage home management where possible and provide confidence in follow up arrangements for prompt recognition of slowly evolving and delayed presentations of hypopituitarism. In the short term, this will have training and learning implications for NHS staff including those in A&E and in GP practice but in the long run will be beneficial to the provision of inpatient capacity, appropriate radiology investigations, prioritisation of virtual and in-person outpatient consultations and prediction of disability.
National priorities	No National Service Framework or white paper identified but this does not detract from priority as brain injury in children and adults is a public health problem worldwide.
Current evidence base	No evidence was identified
Equality considerations	The research recommendation is relevant to groups of people who live with health

	inequalities and those with disabilities limiting their access to optimal healthcare.

K.1.3 Modified PICO table

Population	Inclusion: Infants, children and adults with head injury who are being screened for hypopituitarism: • 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 and stratify by GCS severity: score • Mild GCS 13-15 • Moderate GCS score 9-12 • Severe GCS score 3-8 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.
Intervention	Investigation for hypopituitarism in acute phase Strata: 1. In ED 2. Admission in hospital but not in ED 3. After discharge, within 1 year of injury All timepoints are relevant for investigations for hypopituitarism 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, and sex hormones in adults (LH, FSH, oestrogen or testosterone). 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. Adults may also have growth hormone deficiency caused by traumatic brain injury and would require dynamic stimulation tests. Any deficiency would require subsequent treatment with growth hormone replacement.
Comparison	Investigation for hypopituitarism in chronic phase:

	≥1 year after injury
Outcome	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality • Quality of life (all validated quality of life scores). • Need for treatment of hypopituitarism (growth rate for children will be covered here) • Time to treatment of hypopituitarism • Return to work/return to school Outcomes should enable cost effectiveness to be evaluated for example to include the incidence of hypopituitarism at different time points. Same outcomes applicable to both adults and children. All-follow-up times will be considered.
Study design	Randomised controlled trials or prospective cohort study: Key confounders: Adults: • Extent of extra cranial injury (other organ support) Children: • Extent of extra cranial injury (other organ support) • Age (in children- young child not in adults)
Timeframe	Medium term – to be completed before the next update of this guidance
Additional information	None