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STUDY PROTOCOL

Title: Evaluating eating behaviours, energy homeostasis and obesity in childhood craniopharyngioma: A feasibility study

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Lay summary:
Craniopharyngioma, although a non-malignant brain tumour, causes major health problems because of its location. It is near vision nerves, the pituitary gland controlling many hormones, and brain centres controlling appetite. Treatment involves surgery and radiotherapy, which can cause further damage. Obesity and associated long-term risks are common, and the reasons are complex. Through this project, we will investigate obesity in young people with craniopharyngioma. We want to find out if obesity is related to overeating from a lack of feeling full, appetite hormones not functioning or low metabolic rate. First, we will assess whether patients and their families are prepared to take part in research. Second, we will investigate which tests are best to use. We will measure the brain's response to food cues using special MRI scans and appetite hormones levels in the blood, as well as metabolic rate and questionnaires on quality of life and typical eating. Patients will eat lunch, so we can assess food choice and portion size. These measures will be analysed in relation to each patient's craniopharyngioma severity and treatment, number and type of hormone problems and level of obesity. Although craniopharyngiomas are rare (1-2 new childhood patients/per year in the South-west), this project has the potential to identify novel interventions. It will make a real impact to improve quality of life and health in craniopharyngioma patients with unmet complex needs related to obesity.

These projects could also help us understand how weight problems could develop after other brain injuries.

Background Information

Craniopharyngioma is an embryological tumour with low grade histological malignancy found in the hypothalamus and/or pituitary region. Incidence is between 0.5 to 2.0 cases per million persons per year (1) with 30-50% diagnosed in childhood or adolescence(2)(3). Survival rates are high, with over 98% survival reported (4), but with significant levels of morbidity.

The main long-term sequelae following treatment or due to the tumour itself, includes hypopituitarism, obesity, visual impairment, and neuropsychological deficits. Most patients with craniopharyngioma (85-95%) have multiple pituitary hormone deficits following treatment (5, 6). Obesity is a common feature of children with craniopharyngioma (50%)(7), which may develop several years before diagnosis (8), though there is a marked increase in prevalence (22-62%) following surgery (9, 10). This contributes to longer term risk of metabolic and cardiovascular disease in patients with craniopharyngioma(11). Hypothalamic involvement of the tumour or damage to the hypothalamus following treatment is associated with severe obesity (7) and **the degree of obesity is positively correlated with extent of hypothalamic damage(12)**. Therefore, whilst is a relatively rare disease, the tumour and subsequent treatment have a substantial effect on the health and quality of life (14) of affected patients and families. However, currently there is limited evidence for effective weight loss interventions(15) and pharmacological treatments(16) in this population. Novel interventions based on a greater understanding of the possible impact of craniopharyngioma on eating behaviour are required.

However, mechanisms leading to obesity and altered energy homeostasis are complex, yet largely understudied, in craniopharyngioma. Damage to the hypothalamus from the tumour or treatment affects peripherally secreted hormones (leptin, ghrelin, insulin): elevated leptin (17) and insulin(18) have been reported compared to patients with simple obesity. Hyperinsulinaemia and autonomic imbalance is thought to contribute to hypothalamic obesity in these patients(19). Reduction in energy expenditure is another feature of craniopharyngioma and may be mediated by damage to efferent sympathetic nervous system pathways in the hypothalamus. Additionally, hypothalamic communications with higher brain centres in the cerebral cortex and the limbic system are affected which potentially alter food reward and eating behaviour.

Functional MRI (fMRI) can be a useful tool in the study of obesity (20). Previous studies in obese children demonstrate hyperresponsivity to food cues in the prefrontal cortex (21). A small pilot study of four patients with craniopharyngioma and four controls demonstrated a trend towards higher activation of bilateral nucleus accumbens, bilateral insula and medial orbitofrontal cortex following a test meal in patients suggesting that perception of food cues maybe altered in this population (22).

The hyperphagia and obesity in children and young people with craniopharyngioma causes substantial person and parental worry (14). There is an urgent need to understand the

aetiology of hyperphagia, weight gain and obesity in these children and young people so that therapeutic solutions can be found. This works directly complements the eating behaviour studies already being undertaken in BRC Nutrition (23,24)**.**

Study Objective

The primary research question is whether functional neuroimaging and measurement of appetite hormones are useful tools to investigate hypothalamic obesity and eating behaviour in patients with craniopharyngioma.

This study aims to investigate the feasibility of postulated methods of measuring appetite hormones, metabolic rate, neural response to food cues, and to characterise potential disruption between the hypothalamus and cortical limbic system in patients with craniopharyngioma. The insights gained from this feasibility study will inform a future multicentre trial to investigate the safety, efficacy and cost of a novel intervention in patients with craniopharyngioma to address their eating behaviour and obesity.

Objectives

1. Characterise the severity of the tumour, treatment and pituitary dysfunction in the studied craniopharyngioma patient population.
2. Assess whether sufficient patient numbers can be recruited.
3. Assess patient tolerability of the number and nature of measures used in the study.
4. Investigate which measures are the most informative to elucidate the nature of eating behaviour in those with craniopharyngioma-related obesity.

Study Site

The study will be based at Bristol Royal Hospital for Children and Clinical Research and Imaging Centre (CRICBristol), University of Bristol. Participants will also be recruited at the University Hospitals Wales in Cardiff, and two new Patient Identification Centres (Oxford and Southampton), and be invited to come to CRIC Bristol to take part in the study. The study session will be scheduled at a mutually convenient time for each participant and travel expenses (including an overnight stay if required) will be reimbursed.

Subjects and Recruitment

There are approximately 40 patients known to the Bristol and Cardiff endocrinology teams with craniopharyngioma under 25 years of age. Of these, we aim to recruit a minimum of 20 patients from paediatric endocrinology in Bristol and Cardiff (Dr Crowne and Professor Gregory respectively) and from young adult after-care service in Bristol (Dr Rachel Cox/Ruth Elson). From 2020 onwards, we have added two new Participant Identification Centres (PICs): Southampton Children's Hospital and Oxford Children's Hospital. These centres will identify patients from their databases who fit the criteria for participation and will send out the invitation and appropriate PIS, as per the recruitment details below. The clinical nurse specialist in Bristol will be the main clinical contact for the study.

Recruitment

1. Potential volunteers who have been treated for craniopharyngioma at Bristol or Cardiff will be identified by their treating clinicians. The lead consultants at each site are Dr E

Crowne and Professor J Gregory respectively. Clinicians may use Trust-specific electronic medical records to identify possible volunteers. These records are on NHS trust servers with access provided only to treating clinicians.

2. Potential volunteers will receive an invitation letter from their treating consultant as well as age specific information sheets and parent information sheets for children under the age of 16 years. These documents will be sent by their treating clinician at least 2 weeks prior to their next appointment at the respective endocrinology clinics at University Hospital Bristol NHS Foundation Trust and University Hospital of Wales, so families have time to consider whether they wish to be involved.
3. The invitation letter will have the number to call the local clinical nurse specialist in case the patient/family would like any further information and/or to register their interest in the study.
4. Once they have indicated their interest, one of the research team will then telephone the family to confirm that they would like to participate and to answer any further questions they may have.
    a. If they would like to participate, the caller will:
        i. go through the screening form to ascertain if the patient is eligible to take part screened according to the inclusion and exclusion criteria.
        ii. If eligible, the consent and assent forms (as appropriate) will be posted out to be returned to Site in the stamped addressed envelopes provided, or to be brought to the data collection session if there is insufficient time prior to the appointment. If the parent/participant has any questions regarding the consent process, this can be clarified over the telephone or at the next clinic appointment. For children under the age of 16, consent forms will be signed by the parent, and an assent form will be signed by the child.
        iii. The appointment will then be made with the parent/participant to attend the data collection session at CRICBristol.
        iv. Travel arrangements will then be discussed. We are able to offer travel expenses (if travel receipts are provided), and for those patients travelling from further afield we are able to offer car parking and/or overnight accommodation in the local Premier Inn for the night prior to the session (due to the early start).
        v. The participant will also be asked to fill in the food preference questionnaire online prior to the appointment. The clinician will ask for permission to email the link and instructions to the participant. If the participant does not have any access to the internet, an additional appointment will be made for them to visit CRICBristol to fill in the questionnaire using a University computer.
5. This appointment, and all the details discussed over the telephone, will then be confirmed through a letter (see attached appointment letters: written either to the parent/carer or participant directly if 18 years or older), which will either be posted or emailed to the participant (with permission), such that they have all the information they need regarding the appointment.

It will be explained to all volunteers that they may choose to opt out of the study at any time without affecting or altering their medical care.

Inclusion criteria

- patients aged between 7-25 years who have a diagnosis of craniopharyngioma

Exclusion criteria

- clinically unwell requiring hospital or intensive treatment
- unwilling to fast
- patients for whom it would be unsafe to have an MRI including those with:
    - certain metal implants
    - tattoos with metallic ink
    - metal body piercings which cannot be removed
- pregnancy to avoid harm to the foetus
- claustrophobia in the closed MRI environment or unable to tolerate the MRI scanner
- weight above 152kg and/or girth greater than 210cm due to size limitations of MRI scanner

Sample size determination

The total number of patients with craniopharyngioma patients aged 7-25 years known to University Hospitals Bristol and University Hospitals Cardiff is 40. We aim to recruit a minimum of 20 patients. While this is a small number, this study is primarily one of feasibility. If the measures are well tolerated by participants and important correlations extrapolated, we will use these findings to inform the design of larger multi-centre trials into eating behaviour and obesity in craniopharyngioma.

Withdrawal of participants

Participants are free to withdraw at any time during the study without any impact on their medical care.

Control Group

For every patient with craniopharyngioma, we aim to recruit two healthy matched controls. Both the control participants will be of the same gender and general pubertal stage as one of the patients with craniopharyngioma. Pubertal stage will be assessed at study visit by asking patients and their parents if they have started puberty, and if girls, whether they have started their periods and if boys (age 14-18years) if they have finished growing. Patients will be classified into one of three pubertal stages: pre-pubertal, pubertal, post-pubertal. One control will be of a healthy weight (BMI: range > -2SDS to < +2SDS) whereas the other control will be obese (using BMI SDS cut-off of 95% centile, > 2 standard deviations from the mean).

Recruitment: Control participants will be recruited for this study using a variety of methods: (i) patients with craniopharyngioma who have already participated in our study will be asked if any of their friends or siblings may consider participating ('Best-friend' model); (ii) visit local primary and secondary schools (who have indicated an interest in research) and ask if they would be prepared to send out invitation letters to the parents of children in the appropriate age groups; (iii) advertise the study on various University online forums in case academics at the university have children who might be interested in participating.

Inclusion Criteria: Young people between the ages of 7-25 years old that are sex and general pubertal stage matched with one of the craniopharyngioma patients. Two participants will be recruited for each patient: one will be of healthy weight (BMI > -2SDS to < +2SDS) while the other will be obese (BMI > 2 SDS).

Exclusion criteria: unwell requiring hospital or intensive treatment; unwilling to fast.

Randomisation

Randomisation is not applicable to this study as we are investigating craniopharyngioma patients and a matched-control group only and no intervention is involved.

Study Design, Procedure and Measures

The procedure for the control group will be identical to that for patients with craniopharyngioma, except that the control group will not have an MRI scan or blood tests as part of the oral glucose tolerance test.

Craniopharyngioma patients and control participants will initially be asked to complete an online questionnaire at home about on food preferences. This is to tailor the foods shown to each participant during the food-cue reactivity task completed in the MRI scan for the patients or in the clinic room for the participants. The survey should take a maximum of 45 minutes to complete and can be filled in at home on a computer or smart phone and includes all the simple instructions required.

Each volunteer will participate in the study over the course of a single morning at CRIC Bristol.

After an overnight fast (from midnight), participants will receive the following measures:

1. (Patients & Controls) Assessment of resting metabolic rate using indirect calorimetry (Cosmed K4b2). This is a hand-held device that is first calibrated to the testing room and participant. Participants breathe into a facemask for a short period of time (max 20 minutes including calibration) (25) while sitting upright to measure gas exchange (oxygen uptake and carbon dioxide output).
2. (Patients & Controls) Anthropometrics: Height and weight will be measured to calculate body mass index standard deviation score (BMI-SDS) by the same members of the project team (KN or EH). Body composition will be measured (multifrequency bioelectrical impedance, Tanita MC-780), to give fat-free mass and fat mass, and total body water.
3. (Patients & Controls) Consume a glucose drink (polycal) according to weight.
4. (Patients only) Appetite hormone assessment during an OGTT. Blood samples will be taken via an intravenous cannula at baseline, 30, 60, 90 and 120 minutes post glucose consumption to measure glucose, insulin, ghrelin, GLP1 and PYY. Leptin will also be measured at baseline as well as a full blood count (FBC) and electrolytes (U&Es). The cannulation and blood sampling will be done by members of the research team who are trained and experienced in cannulation and venipuncture.

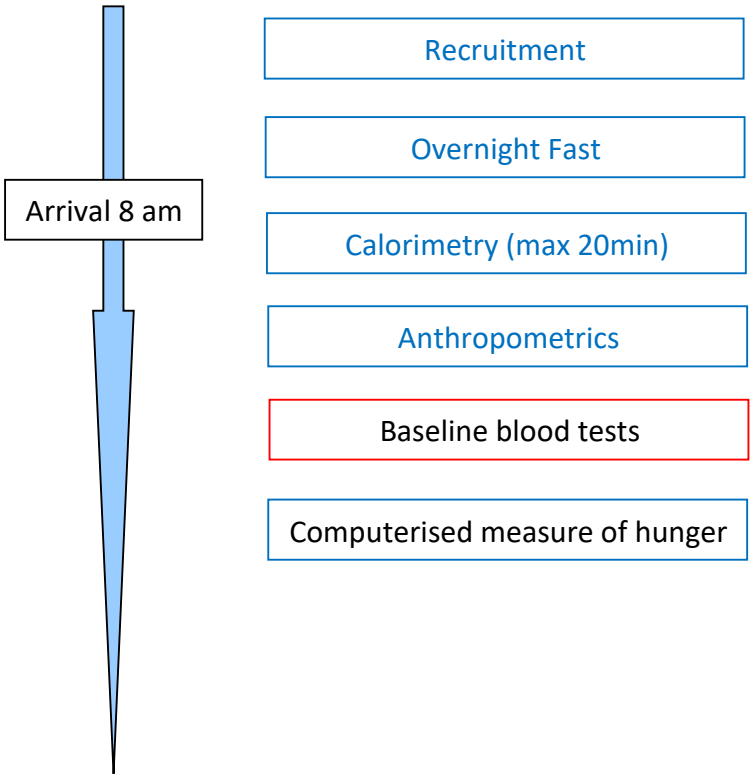
a. As per CRICBristol SOP, usually a maximum of three attempts will be made to cannulate the patient, unless the patient allows another member of the team to try.
b. Obese patients can be harder to cannulate than non-obese patients, however, we will still continue to scan any patients in whom it is not possible to place a cannula if they wish to continue.
c. A maximum of 8-10ml of whole blood will be collected at the baseline sample (as completing FBC and U&Es, as well as leptin). A maximum of 6-8ml whole blood will be collected at each other time-point. It will be ensured that the minimum amount of blood will be taken, in line with research from WHO (25), using age appropriate sample tubes to ensure only the amount necessary for the tests is collected.
d. Samples will be spun and separated in CRICBristol wet lab (SOP in appendix) and frozen then sent to BRI for longer-term storage at -70 degrees prior to transportation under dry ice to the University of Bristol IMEG group laboratory at Southmead hospital for batch analysis. The samples will be clearly labelled with a key and sufficient, de-identified information. The samples will be transferred according to a pre-arranged plan with the receiving lab so that they are sent by courier under appropriate freezing conditions and when the lab is expecting the samples.

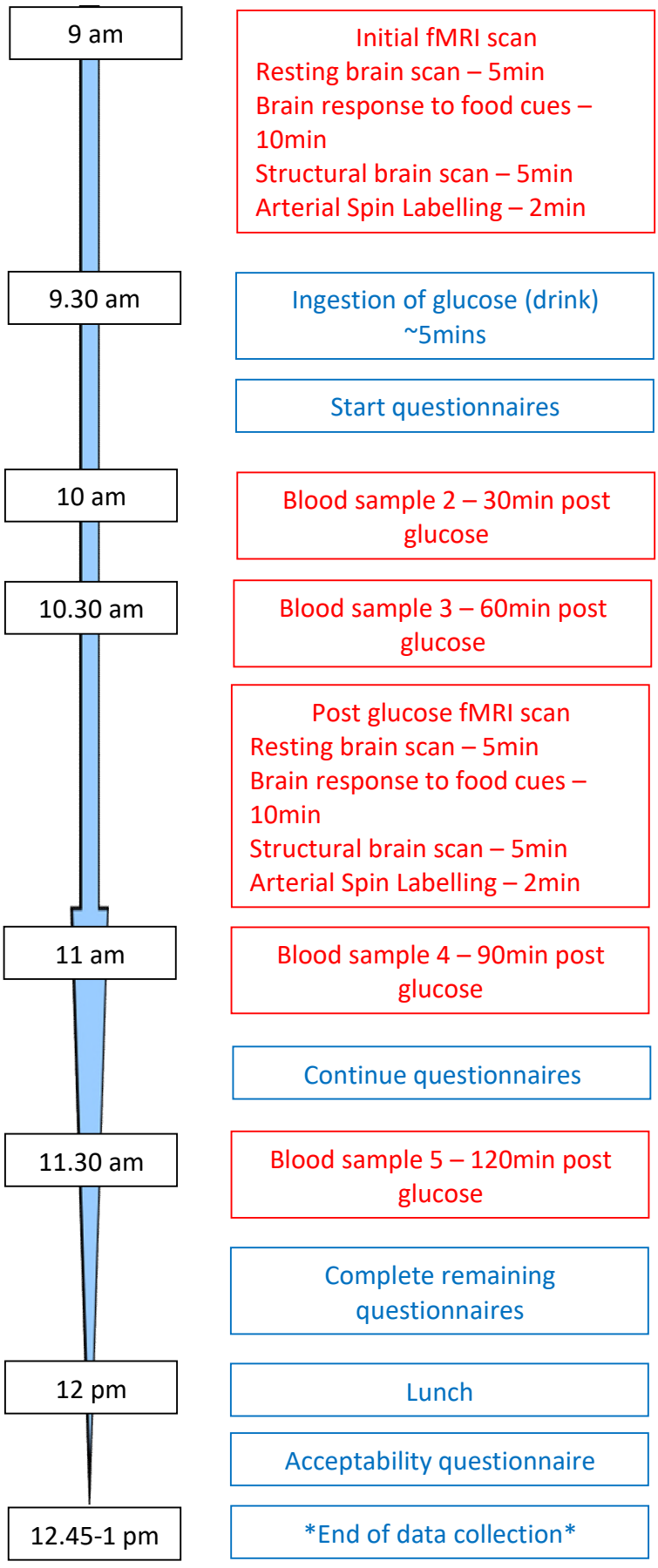
5. (Patients & Controls) Computerised subjective measures of hunger will be taken at baseline, 30, 60, 90 and 120 minutes post glucose consumption.
    a. These are visual analogue scales (, with end points of 'Not at all' and 'Extremely'), accompanied by questions of hunger, fullness, thirst and nausea.
6. (Patients only) The radiographer will conduct the MRI scans. 2 x 30-minute scan blocks: at baseline prior to the glucose drink, and 60 minutes post glucose consumption. Where possible, any MRI brain scans required for patient care will also be done at this time. Each research scan will comprise the following established protocols:
    a. Resting brain scan ~5 minutes
    b. Brain response to food cues - ~10 minutes
    c. Structural brain scan ~5 minutes
    d. Arterial spin labelling scan to quantify blood flow ~2 minutes
7. (Controls only) Food cue reactivity task on the laptop in clinical room.
8. (Patients & Controls) A clinical questionnaire to assess 'Hyperphagic behaviours, drive and severity' (27).
9. (Patients & Controls) Quality of Life questionnaires: SF-36 (28) (validated for adults) and MMQL (cancer survivors under 18 years) (29)
10. (Patients & Controls) Child or Adult Eating Behaviour questionnaire (30, 31)
11. (Patients & Controls) Food intake: *ad libitum* lunch to measure dietary intake. The ad lib lunch may comprise hot and cold items along with a selection of beverages.

The total energy in the meal will be up to 20MJ. Each meal item will be covertly weighed before and after the meal for calculation of energy and macronutrient intake. Participants will be asked to eat alone until they are comfortably full, within approximately 30 minutes.

12. (Patients & Controls) A questionnaire regarding acceptability of data collection (included in appendix).

Figure 1: Study Design Flow Chart (with approximate timing). Items in blue will be completed by patients and controls and items in red will just be completed by craniopharyngioma patients.




9 am
Initial fMRI scan
Resting brain scan – 5min
Brain response to food cues – 10min
Structural brain scan – 5min
Arterial Spin Labelling – 2min
9.30 am
Ingestion of glucose (drink) ~5mins
Start questionnaires
10 am
Blood sample 2 – 30min post glucose
10.30 am
Blood sample 3 – 60min post glucose
Post glucose fMRI scan
Resting brain scan – 5min
Brain response to food cues – 10min
Structural brain scan – 5min
Arterial Spin Labelling – 2min
11 am
Blood sample 4 – 90min post glucose
Continue questionnaires
11.30 am
Blood sample 5 – 120min post glucose
Complete remaining questionnaires
12 pm
Lunch
Acceptability questionnaire
12.45-1 pm
End of data collection

Statistical Plan

Primary measures:

The primary outcomes are to assess the feasibility of

(i) recruitment (no. of participants recruited)

(ii) fMRI (neural response to food cues; resting BOLD signal; brain perfusion) and measuring metabolic rate in young people with craniopharyngioma

(iii) adherence (no. of participants who complete the full data set)

(iv) acceptance of the measures and protocol by participants and their parent/carer (acceptability questionnaire).

Secondary measures:

Data on each of the measures taken:

(i) FMRI measures (as above)

(ii) *Metabolic rate: oxygen uptake and carbon dioxide output

(iii) *Body composition: fat mass; fat-free mass; total body water; height; weight; BMI SDS

(iv) Appetite hormones during OGTT (glucose, insulin, ghrelin, GLP1 and PYY measured at baseline, 30, 60, 90, 120 mins post glucose ingestion)

(v) Leptin, full blood count (FBC) and electrolytes (U&Es)

(vi) *Subjective appetite measure at baseline, 30, 60, 90, 120 mins post glucose ingestion

(vii) *Questionnaire measures: hyperphagia; quality of life; eating behaviour

(viii) *Portion size (in grams and kcal) and food choice during *ad libitum* lunch

(ix) *Food preferences from online questionnaire

(x) Data from the new matched control group for the indicated measures (*) above for comparison with patients.

The above measures will be summarised using means (or medians), standard deviations (or ranges) and percentages where appropriate. Data will be analysed using SPSS version 24.
Pre-processing and analysis of the neuroimaging data will be conducted using FSL (FMRIB's Software library) tools. Analysis of the fMRI data will include: (i) comparison the response to food cues following fasting to following energy consumption using a general linear model; (ii) analysis of functional connections between hypothalamus and cortical regions using the resting BOLD data; (iii) correlations between brain responses and peripheral hormone levels.

Comparison data: Anonymised aggregated data is available for OGTT/food cue reactivity fMRI and appetite hormones data using the same protocol at CRICBristol in obese (n=23) and normal weight adolescents (n=10) (Hinton et al., 2018; BMC Paediatrics). Comparative data is also available for the resting state scans from another study at CRICBristol in healthy weight young adults (n=20) (Hawton et al., 2019 Nutrients). Data from the new matched control group will used for comparison for the measurement of metabolic rate using indirect calorimetry, eating behaviour questionnaires and *ad libitum* meal.

Ethical considerations and informed consent

We understand research in children and young people has significant ethical considerations. We are aware of the need for the application of rigorous ethical principles in the design in the conduct and dissemination of the study. The morbidity associated with obesity and disordered eating patterns in craniopharyngioma poses substantial, long term health risks and

impaired quality of life. There is an urgent need to investigate the pathophysiology of hypothalamic obesity in this patient group to find therapeutic solutions. This has been highlighted as a major gap in evidence in the forthcoming National Rare Paediatric Endocrine Tumour Guidelines: Craniopharyngioma (H Spoudeas, Project Board Chairman, personal communication). Our initial PPI has confirmed the importance of this area to the families affected by craniopharyngioma and a key aspect of this feasibility study is to involve patients with craniopharyngioma and their families in informing the next stage of the research project. Paediatric research projects are commonly criticised for relying on parent report data only (13).

The study will be conducted to protect the human rights and dignity of the participant as reflected in the 1996 version of the Helsinki Declaration. In order to protect the study participants the following provisions will be made/upheld; the study has been designed to minimise pain, discomfort and fear and any foreseeable risk in relation to the treatments involved; the explicit wishes of the participant will be respected including the right to withdraw from the study at any time; the interest of the patient will prevail over those of science and society; provision will be made for indemnity by the investigator and sponsor.

We will endeavour to do any routine blood tests required for clinical care (usually required every six months) with the blood sampling for this study such that volunteers are not subjected to an extra episode of cannulation, and where the time interval is appropriate, to do their clinical scans at the same time as the research study MRI (not applicable to control group).

This protocol and associated documentation will be reviewed by a REC through the HRA/IRAS system.

Anticipated benefits and risks

Benefits: The findings from this study may offer significant positive benefits for patients and families of those affected by childhood craniopharyngioma. The eating problems and associated obesity are often expressed to be some of the most distressing and impact the greatest on quality of life (14). Hypothalamic obesity has multiple deleterious effects on metabolic and cardiovascular health. By better understanding the neuroendocrine pathways linked to obesity in these patients, we have a greater chance of developing a framework for intervention which can then be tested through RfPB grants. Such interventions might possibly include eating behaviour modifications, appetite hormone modulation, or new therapeutics coming on stream such as Setmelanotide (MC4R agonist). Identifying any links between obesity/eating behaviour and preceding craniopharyngioma presentation or management may lead to less impactful primary treatment strategies, or early interventions of those particularly at risk.

Specific benefits to volunteers includes the potential for early detection of insulin resistance or diabetes from the oral glucose tolerance test (not applicable to control group). They may also gain an understanding into their own eating patterns and responses to food cues, which may help in identifying strategies to control weight gain.

Risks (not applicable to control group)*:* Blood sampling poses some risk of minor bruising at the cannulation site, as well as the possibility of more than one attempt in case of difficult venous access. All care will be taken to minimise distress. All participants will usually require 6 monthly blood tests as part of their standard clinical care. We will endeavour to do any routine blood tests required for clinical care with the blood sampling for this study such that volunteers are not subjected to an extra episode of cannulation.

The fact of additional tests, such as the OGTT, may lead to anxiety around the results. Volunteers and families will be counselled about the management strategies in case any results are abnormal and that these results will be communicated to them via their clinical team.

The closed environment and/or the noise of the MRI may cause anxiety. However, all craniopharyngioma participants will have had previous scans and be having regular follow-up MRI scans and will be familiar with MRI scans. We will provide them with clear details of how to signal distress when in the MRI with the option to withdraw at any point before, during or after the scan. It is unlikely that the study MRI will find previously undetected structural anomalies, as all of the volunteers would have had previous scans and have a programme for follow-up scans, as part of their craniopharyngioma management. But it might detect a change in their craniopharyngioma – but this would be very relevant to their clinical care. Any new abnormalities or change in their craniopharyngioma detected will be discussed with them through their clinical team.

Informing participants of benefits and risks
Participants will be informed of the benefits and risks of the study through age specific participant information sheets (PIS). Parents will be provided a PIS whilst the children and young people will also be provided appropriate information sheets. Age-banded PIS for participants will be provided in the following categories: 16 years and over, 10-15 years and under 10 years. Prior to consenting, participants and families will have the opportunity to discuss the trial with their clinician or principal investigators in person or by telephone, depending on family preference. Any new information that arises during the course of the study which may affect participant willingness to take part will be communicated directly to volunteers and families.

Obtaining informed consent
All participants will need to provide written consent for the study as a whole and specifically for the fMRI imaging. Young people aged 16 and over will sign the consent forms themselves. Parents and children under 16 years will sign the consent form and children will sign an assent form. The age appropriate PIS will contain information about the study process and participants will have the opportunity to discuss the study with the research team and seek clarification about any questions they may have.

Data Management
Confidentiality: Data collected will initially be kept confidentially on password-protected NHS secure servers within the clinical and research team. All data anonymised for analysis and subsequently for publication and will be backed up on both University of Bristol and UHBristol servers for security. No identifiable patient information will be published or disseminated.

Case report forms: CRFs will be the proforma used for each patient to record clinical details of their treatment history etc, and to record details of the data collection during the session at CRICBristol.
Records retention: Records will be retained for 10 years in line with the current Data Protection Act. Paper records will be stored in a locked filing cabinet.
Auditing and inspection: Records will be made available for inspection if required.

Adverse Event Reporting

This study will record and report details of any Serious Adverse Events (SAEs) that are required to be reported to the Research Ethics Committee (REC) under the terms of the Standard Operating Procedures for RECs. This will be in accordance with the UHBristol safety reporting procedure. UH Bristol undertakes this role on behalf of the University of Bristol.
An SAE is defined as a 'related'* and 'unexpected'** untoward occurrence that:
(a) Results in death;
(b) Is life threatening;
(c) Requires hospitalisation or prolongation of existing hospitalisation;
(d) Results in persistent or significant disability or incapacity;
(e) Consists of a congenital anomaly or birth defect; or
(f) Is otherwise considered medically significant by the investigator.

* 'related' is defined as: resulting from the administration of any research procedures.
** 'unexpected' is defined as: a type of event not listed in the protocol as an expected occurrence.

In the context of the current study, an occurrence of the type listed in (a) to (f) above will be reported as an SAE only if it is suspected to be related to an aspect of the research procedures, or it is an unexpected occurrence. If it is considered both related and unexpected, it will be classified as a SUSAR – Suspected Unexpected Serious Adverse Reaction.

A member of the project team should be informed of the SAE by telephone. They will inform the Chief Investigator (CI), who will jointly decide if the event should be reported to the main REC and the study Sponsor as an SAE. SAEs and SUSARs will be reported to the Sponsor as per the Research Safety Reporting Protocol of the UH Bristol. The standard operating procedure (SOP) for adverse event reporting can be found at the following link from the University of Bristol: http://www.uhbristol.nhs.uk/research-innovation/information-for-researchers/setting-up-and-running-a-clinical-research-study/what-to-do-when-approval-is-received/safety-reporting-(adverse-events)/.

Sponsorship and Insurance

This study will be conducted under the sponsorship of the University of Bristol. Insurance will be organised by the University of Bristol.

Publication Policy

As this project will be conducted through the NIHR Bristol BRC Nutrition theme, the BRC publication policy will be followed. Any manuscripts resulting from this project will be published in open access journals only, and the appropriate affiliations will be acknowledged.

Study Personnel and their primary roles

Dr Elanor Hinton - Chief investigator; study design and development; data collection and analysis; supervision of KN (research)
Dr Liz Crowne – Lead clinician; study design and development; recruitment of paediatric patients in Bristol, consenting patients; supervision of KN (clinical)
Dr Fiona Lithander – Research dietitian; collection and analysis of metabolic rate data; design of test lunch
Prof Julian Hamilton-Shield – clinician; BRC Nutrition childhood workstream lead; study design and development
Dr Kruthika Narayan – Paediatric specialist endocrine trainee; recruitment, consenting patients, data collection and analysis
Mrs Ruth Elson – Clinical Nurse Specialist; explaining the study, patient contact
Dr Rachel Cox – clinician; recruitment and consent of adult patients in Bristol
Ms Rachel Perrow – Clinical Nurse Specialist; explaining the study, patient contact
Prof John Gregory – clinician; recruitment and consent of paediatric patients in Cardiff
Dr Justin Warner – clinician; recruitment and consent of paediatric patients in Cardiff
Ms Aileen Wilson – Lead Research radiographer CRICBristol
Prof Jeff Holly / Dr Claire Perks / Ms Kalina Biernacka – from IMEG group at Southmead hospital. Advising on appropriate assays and sample collection SOP; assays to analyse appetite hormones and providing the results.
Ms Nimra Naeem – BSc intercalating medical student; data collection and analysis
Dr Madeleine Adams - Locum Consultant in Paediatric Oncology; recruitment and consent of paediatric patients in Cardiff
Ms Rebecca Crook – MSc Applied Neuropsychology student; data collection and analysis
Dr Tashunka Taylor-Miller – Paediatric specialist endocrine trainee; recruitment, consenting patients, data collection and analysis
Ms Sophie Szymkowiak - MSc Applied Neuropsychology student; data collection and analysis
Dr Hanna Zielinska, Rachel Barker and Georgina Kingshott – blood sample processing and analysis
Dr Fiona Ryan - Consultant in Paediatric Endocrinology, Oxford Children's Hospital. Identification of paediatric patients in Oxford.
Dr Nikki Davis - Consultant Paediatric Endocrinologist And Diabetes Specialist, Southampton Children's Hospital. Identification of paediatric patients in Southampton.

Conflicts of interest

No declared conflict of interests for any of the researchers.

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