

**The design and inception of a pilot study assessing the relationship between
migraine and appetite behaviours in a paediatric population**

Thesis submitted in accordance with the requirements of the University of
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Abstract:

Background

An association between migraine and obesity has been identified. Currently no causality has been identified. Certain appetite behaviours put individuals at increased risk of obesity. Appetite behaviours have not been thoroughly examined in the paediatric migraine population. Work has shown that migraineurs crave carbohydrates around time of attack, that anorexia can exacerbate a migraine and that migraineurs often avoid certain foods that supposedly trigger their migraine. Hitherto no formal study of trait appetite behaviours in migraineurs has been conducted. Theoretically, aberrant appetite behaviours in migraineurs may mediate the onset of obesity.

Aims

The aims of this study were multiple. Firstly, it was to undertake a formal literature review into the area of the relationship between migraine and obesity. Secondly it was to design a study assessing the relationship between migraine and appetite behaviour. Thirdly it was to examine, within the study, the feasibility and utility of the recruitment process and the psychometric tools respectively.

Methods

The study was a pilot, cross-sectional questionnaire based study. Migraine patients were recruited from the tertiary paediatric clinics at Alder Hey Children's Foundation Trust Hospital. *Inclusion criteria* were a diagnosis of migraine based on clinical criteria by the treating paediatrician; participants were aged between 5 and 16 years, including both sexes; participants were new referrals to Alder Hey neurology department and were migraine medication drug naïve. *Exclusion criteria* were that children were under 5 years old or over 16 years of age; or had a known presence of secondary cause of migraine-like headache e.g. brain tumour. Specific psychometric tools were utilised as the primary and secondary outcome measures for predicting migraine severity, appetite behaviour, food cravings, food intake and behavioural psychology. All of these psychometric tools were answered at a one off interview with the participants.

Results

A comprehensive literature search and thorough study design were achieved, with the study gaining ethical and site-specific approval. The limited sample size gained from the early recruitment phase prevents insights into the relationship between migraine and appetite behaviour. A great deal about recruitment utility and suitability of psychometric tools was gleaned from early stages of recruitment.

Conclusion

Drawing robust conclusions about the relationship between appetite behaviour and migraine from this study is not possible. There are, however, some interesting preliminary results about the study design and tools of the study. Recommendations were designed to improve the study design in response to the qualitative findings, in order that robust quantitative findings can be elucidated when the study is continued to completion.

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Glossary:

AADA	Aromatic L – amino acid decarboxylase
ALSPAC	The Avon longitudinal study of parents and children
AN	Anorexia nervosa
ANOVA	Analysis of variance
BMI	Body mass index
BMI z-score	Body mass index z-score
BN	Bulimia nervosa
BOLD	Blood Oxygen Level Dependent
CACNA1A	Voltage – dependent calcium channel alpha 1
CBCL	Child behaviour checklist
CCK	Cholecystokinin
CDH	Chronic daily headache
CEBQ	Children’s eating behaviour questionnaire
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
CRF	Corticotrophin releasing factor
CRP	C-reactive protein
CSD	Cortical spreading depression
CSF	Cerebrospinal fluid
DD	Desire to drink
DEBQ	Dutch eating behaviour questionnaire
DEBQ – c	Children’s Dutch eating behaviour questionnaire
DXA	Dual energy X-ray absorptiometry
EE	Energy expenditure
EF	Enjoyment of food
EI	Energy intake
EO	Emotional overeating
EU	Emotional undereating
FCI	Food cravings inventory

FF	Food fussiness
FIQ	Food intake questionnaire
fMRI	Functional Magnetic Resonance Imaging
FR	Food responsiveness
FTO	Fat mass and obesity associated gene
G.P	General practitioner
HIT-6	Headache impact test – 6 score
H1	Histamine receptor 1
IHS	International headache society
IOTF	International obesity task force
LORN	Liverpool Obesity Research Network
LREC	Local research ethics committee
MIDAS	Migraine disability assessment score
MRI	Magnetic Resonance Imaging
MSG	Monosodium glutamate
NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NPY	Neuropeptide Y
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
OX1	Orexin receptor 1
OX 2	Orexin receptor 2
pCPA	p-Chlorophenylalanine
pedMIDAS	Paediatric migraine disability assessment score
PET	Positron Emission Tomography
P3MC	A double blind three arm parallel group randomized placebo controlled trial of propranolol and pizotifen in preventing migraine in children
R&D	Research and development department
RCT	Randomised control trial
relBMI	Relative body mass index

SE	Slowness in eating
SNRI	Serotonin noradrenaline re-uptake inhibitor
SR	Satiety responsiveness
STROBE	Strengthening the reporting of observational studies in epidemiology
TPH	Tryptophan hydroxylase
5-HT	Serotonin
5-HIAA	5-hydroxyindoleacetic
U.K	United Kingdom

Chapter 1: Introduction:

Chapter 1: 1 what is migraine?

1.1.1 Definition and prevalence of migraine

Childhood headaches are a very common paediatric problem. Primary headaches are those in which there are episodic headaches in the absence of a structural cause. Paediatric migraine is the most prevalent primary headache(1). Migraine has a childhood prevalence of 9.7-10.8% in school age children(2-4). Interestingly, migraine prevalence increases with childhood age, being rare before the age of two and as high as 20% in elder adolescence(5). The average age of onset is 6 years old(7), with the prevalence higher in boys until puberty, when the pattern reverses (6). The majority of adults have their first headache diagnosed in childhood or adolescence(5, 6), hence it is clear to see the burden this disease has on the paediatric population. That being said, paediatric headache disorders are considered to be an understudied area(7), with much still to be discovered and understood about the pathogenesis of headaches and, in particular, migraine. Moreover, much is to be revealed about genetic, environmental and crucially neurobiological mechanisms regarding migraine(8).

The international headache society(IHS)(9) for diagnosing migraine (see classification below) highlights that it is based upon positive clinical findings; typically of unilateral headache with features such as nausea, vomiting, photophobia, amongst others. In contrast, another primary headache, namely tension type headache, is classically bilateral, often more mild and without associated features. In the last decade it has been increasingly agreed that each of these headaches share a lot of similar features, and it is now in contention as to whether it is valid, or indeed practical, to classify them as separate entities, or whether they are part of one headache type(10).

Furthermore, headaches can present as chronic daily headaches, whereby headache occurs 15 days a month or more(11). This form of headache is particularly troublesome to diagnose and classify. Headache is one of the commonest referrals from general practitioners to paediatric neurology

making up 27% of referrals (based on an unpublished audit conducted at Alder Hey this year). Clinic populations are patients at the more severe end of the severity spectrum and generally those patients most likely to suffer from co-morbidity.

1.1.2 Diagnosis and classification of Migraine(12)

The two most common forms of migraine are migraine with aura and migraine without aura. The classification of these is below. The classification of chronic migraine and a more through classification of migraine with and without aura are in the appendix (Appendix A).

Migraine without aura

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

- A. At least 5 attacks fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)
- C. Headache has at least two of the following characteristics:
 1. Unilateral location
 2. Pulsating quality
 3. Moderate or severe pain intensity
 4. Aggravation by or causing avoidance of routine physical activity (*e.g.* walking or climbing stairs)
- D. During headache at least one of the following:
 1. Nausea and/or vomiting

2. Photophobia and phonophobia
- E. Not attributed to another disorder

Migraine with aura(12)

Description:

Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
 1. Fully reversible visual symptoms including positive features (*e.g.* flickering lights, spots or lines) and/or negative features (*i.e.* loss of vision)
 2. Fully reversible sensory symptoms including positive features (*i.e.*, pins and needles) and/or negative features (*i.e.*, numbness)
 3. Fully reversible dysphasic speech disturbance
- C. At least two of the following:
 1. Homonymous visual symptoms and/or unilateral sensory symptoms
 2. At least one aura symptom develops gradually over ≥ 5 minutes and different aura symptoms occur in succession over ≥ 5 minutes
 3. Each symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache fulfilling criteria B-D for *Migraine without aura* (above) begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder

1.1.3 Pathophysiology of migraine

The pathophysiology of migraine is complex, and still not completely answered. Migraine is a primary brain disorder, which can cause significant burden. It has been shown to have a strong genetic link(13, 14).

1.1.4 Hyperexcitability

One theory of migraine pathophysiology is that the neurons in the cerebral cortex are hyperexcitable in migraine sufferers(15). Studies have shown, though not unanimously, that there is thus a persistent excitability lending to a susceptibility to migraine in the sufferer(16-18). In a certain type of migraine, namely familial hemiplegic migraine, it has been shown that a calcium channelopathy, caused by a gene defect (the CACNA1A gene(19)) is the cause of the hyperexcitability in neurons. To what extent this is the case in all migraine remains unclear. In migraine sufferers there is a lowered threshold to internal and external stimuli. Certain stimuli can trigger a wave of deregulated cortical function, which can lead to large swings of increased or decreased excitability(20). This is thought to lead to cortical spreading depression (CSD).

1.1.5 Cortical Spreading Depression

CSD is instrumental in migraine pathogenesis. Incidentally discovered over 60 years ago(21), one theory suggests that cortical spreading depression leads to the triggering of a migraine aura and the activation of the trigeminovascular system(22). CSD is a self-propagating, depolarization of neurons and glia. Unequivocal evidence to its exact role is still not clear. Some studies suggest it triggers the trigeminovascular system (see below)(23, 24). What has been shown is that there is “depressed neuronal electrical activity with transient loss of membrane ionic gradients, with massive surges of extracellular potassium, intracellular calcium as well as neurotransmitters(25)”. CSD spread is indiscriminate, and its spread infringes on pial arteries and venous circulation. This leads to a brief

hyperemia, but is subsequently followed by a prolonged oligoemia(22, 26-29). Twenty percent (20%) of migraine sufferers have an aura prior to the onset of a migraine, and it has been proposed that CSD is the cause of the aura(22). A caveat to this is a recent review of a number of cases of patients who had treatment that removed their aura whilst their headache remained, questioning whether CSD is a necessary prerequisite to migraine(30).

1.1.6 The root of pain - peripheral versus central sensitization

The link between CSD and the pain aspect of migraine is still unclear(25). It remains contentious as to whether CSD can cause pain(25); or whether it is CSD triggering the trigeminovascular system or triggering the brain stem itself that leads to pain(24). Until end of the 20th century, it was generally accepted that migraine was a vasogenic pathology.

According to this theory, the pain caused by headache was thought to be due to neurogenic inflammation and dilatation of large cranial vessels and dura mater, mediated principally by CGRP, substance P and neurokinin A(31). It was proposed that this neurogenic inflammation lead to stimulation of nociceptive pathways in the trigeminal meningeal afferents that cause severe pain. In essence, the theory was that pain originates in peripheral nociceptors of meninges and meningeal blood vessels (coined 'peripheral sensitization') due to this sterile inflammation, hypoperfusion and subsequent vasodilatation(31).

There are a number of components to migraine attacks that are not fully explained by the peripheral sensitization/vasogenic theory. Firstly, the vasogenic theory doesn't account for the 'prodromal' symptoms that occur in certain sufferers. Classic prodromal symptoms, such as fatigue or inattention, precede any vascular changes by up to 24 hours(32). Secondly, aura symptomatology can have a wide spectrum within one attack in an individual (with a combination of speech, language and visual disturbances), transcending the known neurovascular boundaries, suggesting that aura isn't completely explained by the vasogenic theory(33). The increasing use of functional imaging has helped improve knowledge of migraine

pathophysiology over the last fifteen years. Positron Emission Tomography (PET) scans of migraine patients whilst in attack, have shown that blood flow patterns don't follow normal neurovascular patterns(34). Furthermore, Magnetic Resonance Imaging (MRI) studies of patients within migraine attack highlighted that reductions in blood flow were not significant enough to cause a degree of ischaemia necessary to explain the migraine symptomatology being experienced by subjects(35).

Further innovative neuro-imaging research has identified a potential alternative migraine pathophysiology. Blood Oxygen Level Dependent (BOLD) Functional MRI (fMRI) studies implicated the midbrain in the generation of migraine attack and pain processing(36). Signal intensity increases were shown in the red nucleus, substantia nigra and periaqueductal grey matter consistently whilst patients were enduring their migraine attack. Further PET scan studies supported this work; in patients with spontaneous migraine attacks (both with and without aura) there were significant increases in signal intensity of the dorsal pons, amongst other areas of the brain stem(37).

These recent neuro-imaging studies suggest that a migraine generator probably exists in the midbrain. This moves away from the concept of a vascular process underpinning migraine pathophysiology and towards the possibility of a neurogenic process being the key to migraine attacks; this theory is being coined 'central sensitization'.

CSD is still implicated in this updated migraine pathogenesis; this has been reiterated by further neuro-imaging studies. It is thought that CSD is still the first step in migraine pathogenesis, leading to brainstem activation(35, 38). It is thought that dysregulation of the brain stem underpins the sensory (particularly nociceptive) modulation of neurovascular afferents.

What remains to be illuminated in migraine pathogenesis is what triggers the pain mechanism? For the majority of the twentieth century it was accepted that vasoconstriction triggered the pain process, whilst modern neuro-imaging implicates the brain stem heavily in migraine pathogenesis.

Subsequently it has been suggested there may be a brainstem generator that triggers the pain process.

It must be noted that the most recent migraine therapy to be trialled successfully, the Calcitonin Gene-Related Peptide Receptor Antagonists, or 'gepants', which successfully abort migraine attacks, have no role in altering the vasculature in a migraine attack, thereby further supporting the central sensitization theory as the originator of migraine pain. Although many feel this model has superseded the vascular model, it remains contentious(39). It is clear to see that a comprehensive unified theory of migraine pathogenesis currently remains elusive.

1.1.7 The impact of migraine

The spectrum of migraine severity, and hence its impact on a sufferer's quality of life, is very wide. Previous work suggests that migraine can significantly reduce the quality of life for migraine sufferers in both school and social functioning(40). Recent work suggests that the majority of paediatric migraine sufferers can be categorised to have a mild disability. Of those migraineurs that present to tertiary clinics, however, a greater proportion have a higher disability level(41); to the degree that migraine limits their curricular and extracurricular ability at least third of the time(42). One study suggests migraine attacks cause school absence in 36.1% of migraineurs(43). No work has hitherto focused on relationships between severity of migraine and amount of school absence.

1.1.8 Migraine transformation

A crucial part of the pathophysiology of migraine is the recent concept that a proportion of migraine sufferers do not have a static disease, but rather a sub-group have migraine transformation. This term means the progression of migraine from low frequency episodic headache leading to high frequency episodic headache and finally to chronic daily headaches. This transformation may cause progression to stroke or the occurrence of brain lesions (due to frank lack of blood flow resulting from spasm of blood vessels(15-17)). It

has, therefore, been accepted that it is crucial that risk factors for this form of headache are highlighted to control or prevent them and hence ameliorate the devastating effects migraine can have if left to progress. Recently it has been shown in adults that a key risk factor for migraine progression is obesity(44). Crucially, this is a potentially modifiable risk factor, unlike age.

1.1.9 Treatment of migraine

Non-pharmacological:

General measures:

Self help strategies have been anecdotally reported to reduce the burden of migraine. These include avoiding stress, good 'sleep hygiene' - regular bedtimes and not watching television directly before bed amongst others. Maintaining good hydration, eating regularly and avoiding known precipitants are beneficial(45).

Behavioural interventions:

Thermal biofeedback, which involves attempting to alter skin temperature by responding to feedback about this temperature, can be used as an intervention. Alternatively, progressive muscle relaxation, or hypnosis and self-administered stress management have been reported to reduce headaches(45). Currently, no direct comparisons of these behavioural techniques versus pharmacological therapy have been conducted. There is little evidence of how successful these treatments are in large migraine populations(46).

Pharmacological treatments:

It should be noted that not all of the treatments (acute relief or prophylactic) for migraine are licensed for use on children(45). Below is a review of the options available for migraine treatment. Those that are unlicensed are noted. The effectiveness of these medications in children is not fully known, simply because randomised control trials (RCT) have not been conducted(45). Two of the most commonly prescribed prophylactic medications, namely Pizotifen and Propranolol, are only currently being compared in an RCT(47).

Treatment of acute attacks:

Simple analgesia:

Paracetamol is often first line therapy(45); it has previously been shown to be twice as likely as placebo to alleviate pain. It can cause hepatic impairment in overdose. Rarely it can also cause rashes and blood disorders. Ibuprofen, a non-steroidal anti inflammatory drug (NSAID), has been shown to have similar efficacy in treating migraine pain as Paracetamol(45). Ibuprofen can cause gastrointestinal upset and even stomach ulceration; other side effects include an hypersensitivity reaction and drowsiness(48). Aspirin is not to be used in children under 16 due to the association with Reye's syndrome(45).

Tryptamines (Triptans):

The 'triptans' are serotonin agonists. They are administered in a migraine attack. They are reserved for patients unresponsive to conventional analgesics(49). Sumatriptan, a nasal spray, is licensed in the United Kingdom (UK) for 12-17 year olds for acute relief/treatment of migraine with or without aura. Nausea, vomiting and tingling/heaviness of neck and chest are reported side effects(49). Alternative triptans include Zolmitriptan, Rizatriptan, and Almotriptan. There are currently no studies in the paediatric population comparing the triptans(45).

Antiemetics:

Ideally administered early after the onset of a migraine attack, antiemetics may reduce nausea and vomiting in older children in whom these symptoms occur regularly. Options of antiemetic include Metoclopramide and Domperidone(50). Metoclopramide has rare but serious extrapyramidal side effects. Other more common side effects are drowsiness, anxiety and restlessness(51). Domperidone has rare side effects of gastro-intestinal upset(52).

Prophylactic treatment of migraine:

Pizotifen:

Pizotifen is an histamine (H1) and serotonin receptor antagonist, it is licensed for the prevention of migraine in children over 2 years old. It is considered to be the first line preventative therapy for migraine, however, it has a number of unwanted side effects. Of particular relation to this study, increased appetite and subsequent weight gain are common side effects(45, 50, 53). Drowsiness is another common side effect.

Propranolol:

Propranolol is commonly used for migraine in children, but is contraindicated in asthmatics(45). Side effects include reduced energy, tiredness and depressive symptoms. Its effectiveness in the treatment of paediatric migraine is not established, in spite of its regular use in the management of migraine(54).

Amitriptyline:

Although there are no randomized control trials of the use of Amitriptyline in the management paediatric migraine, it is sometimes used as a prophylactic migraine medication(45). It can reduce the severity and length of a migraine attack. Sedation is a common side effect of Amitriptyline.

Anti-epileptic drugs:

Increasing evidence is emerging that antiepileptic drugs help reduce migraine morbidity(45).

Topiramate:

In particular, Topiramate is shown be effective in reducing mean migraine frequency(55). A common side effect of Topiramate is weight loss. One study showed that 37% of patients had a mean weight loss of 5.1kg over a period of four months on the drug(56). Another side effect is sensory changes.

Levetiracetam:

No randomized trials have been published about Levetiracetam in paediatric

migraine prophylaxis. It is currently not licensed as a migraine prophylactic medication in children. An open label prospective trial on twenty patients, however, showed 90% of patients had reduced headache frequency and morbidity(22). Common side effects include nausea, vomiting, diarrhoea and dyspepsia(57).

It is clear that the management of migraine is varied. General measures are important such as good sleep hygiene. Consideration of general behavioural interventions, such as muscle relaxation is important. Simple analgesia should be the first pharmacological step, followed, if necessary, by acute relief medication. Prophylactic medication should be reserved for frequent or severe migraine. It is relevant to this author's research that two of the prophylactic medications, namely Pizotifen and Topiramate, have an effect on appetite and weight. Hitherto no study has fully uncovered the mechanisms behind this.

1.1.10 Migraine and associated co-morbidities

Migraine has a number of co-morbidities. These include sleep problems, stress, obesity, appetite problems and depression, amongst others(58). This study aims to focus on one of these co-morbidities, obesity, or more specifically, appetite behaviours that theoretically can lead to obesity. There is much neurobiological overlap between migraine, appetite and obesity that will be explored in chapter 1.4. Furthermore, there is phenomenology that anticipatory stimuli can trigger migraine attacks. This ties in with the hedonic concept of want for foods that will be covered in chapter 1.3. A review of the potential relationship between migraine, appetite and obesity is now necessary.

Chapter 1:2 – What is obesity?

1.2.1 Definition and measurement of obesity

Obesity has been defined as “a condition of excess body fat that may harm health(59)”. In the adult population, overweight is defined as a body mass index (BMI) greater than 25 and obese is defined as a BMI greater than 30 (60). There is no unanimously accepted definition of overweight and obese thresholds in children and adolescents(61), because definition is difficult in this age group(62, 63). Various criteria have been designed to assess overweight and obese status in this age group. These include earlier methods such as measuring triceps skin folds(64), to more intensive methods such as Magnetic Resonance Imaging(MRI)(65). Ultimately, the optimal measurement of paediatric obesity would reflect levels of increased adiposity and associated risk of morbidity(61). An important distinction in measurement of increased adiposity is whether adiposity is measured directly, for example by dual energy X-ray absorptiometry (DXA), or indirectly by weight based measurements such as BMI. Pragmatically, weight definitions, based on simple anthropometric measurements (that have reasonable accuracy) are useful. They can be utilized in a range of settings such as population surveillance and for population studies. In children, however, simple BMI is not an accurate measurement of adiposity across a spread of ages(61). Ratios of lean to fat mass vary in children as they grow(66), particularly around the maturation stage (67).

Thus, it is clear to see, obesity cannot be simply seen as an increase in weight, but rather as an increase in fat mass(68). Arguably, this is no startling revelation, but much early work on childhood obesity did not even accurately define obesity(69). The fact that there are no international agreed thresholds of overweight and obese in this age group, is testament to the arduousness of defining and accurately measuring childhood obesity. Currently, in the United States, the 85th and 95th percentile of body mass index (BMI), which are sex and age specific, are set as cut offs for overweight and obese(70, 71). These are based on national survey data, but are still

criticised as being rather arbitrarily defined cut offs(70). In the U.K, at the turn of the millennium, under an initiative from the International Obesity Task Force(72), there was a focus to formally design a more accurate measure of children's body fat. As such, BMI-z scores have been calculated(70). Essentially, the cut-off scores of adult BMI are linked to children's BMI percentiles. The reference population utilised was from a heterogeneous mix of survey data from several different countries, which had large variations in overweight and obesity prevalence(70). Thus, from these growth centile curves, one can calculate whether a child is overweight or obese, by referring to their age and sex specific international cut-off points for BMI z-scores. The cut-off points, therefore, pass through the BMI of 25 (upper scale of normal weight) and 30 (obese) at age 18(70). In the U.K, BMI-z scores are currently considered the best indirect measurement of adiposity on a single occasion(73). It may not, however, be the optimal measurement for tracking a child's fat mass over time(73). Notably, other less commonly used methods of measuring a children's fat mass include waist circumference, relative BMI, skin fold thickness, bioelectrical impedance and air displacement plethysmography, with the latter mostly utilized in research(59, 71, 74, 75).

1.2.2 Prevalence of Obesity

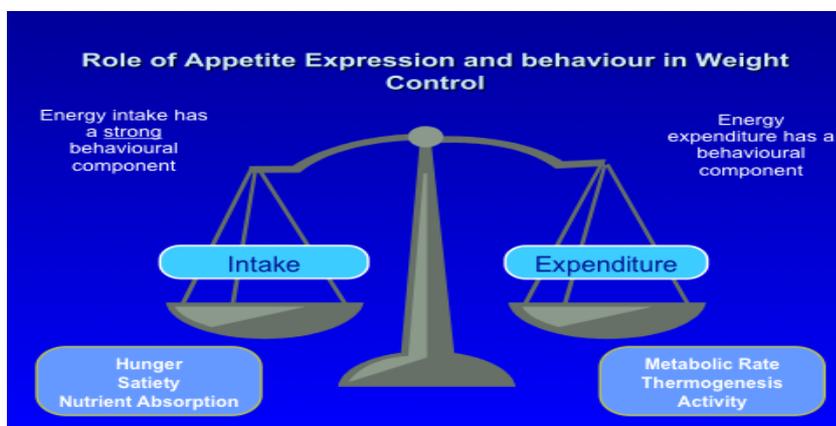
The prevalence of overweight or obese children aged 2-15 in the U.K is 31% and 29% for males and females respectively(56). Latest figures show that, in Liverpool, 26.6% of childhood males are overweight or obese, whilst 31.4% of childhood females are overweight or obese(76). Perhaps most startling is the prediction made in the Foresight report that suggests childhood obesity levels could rise from current levels of 7% to 26% by 2050(58). Furthermore, there are predictions that the future cost to the NHS of weight related disease could rise from £7.1 billion (annual cost in 2001) to £22.9 billion by 2050. The huge health, fiscal and wider societal effects of this escalating problem are simply astonishing. The rapid global increase in obesity prevalence, along with the severity of its pathological consequences, has led to many scientists coining the term "globesity"(71). Thirty percent (30%) of adult obesity starts in adolescence. Unsurprisingly, it has been

comprehensively stated in medical literature that being overweight in childhood or adolescence leads to a high risk of being overweight or obese in adulthood(77). Such ‘tracking’ (an epidemiological focus on ill health over time) is certainly apparent for obesity. Moreover, morbidity due to obesity is occurring even in the childhood years. It is estimated that 80% of obese adolescents have elevated blood pressure(78) and 25% of obese children are predicted to have impaired glucose tolerance(79). There is also emerging evidence that obesity may cause increased risk of childhood asthma(80, 81) and sleep apnoea(82, 83), thus the focus on paediatric obesity prevention is of paramount importance to national health(84). This is not solely necessary to prevent later onset of pathology, but to tackle the morbidity it is causing in childhood.

1.2.3 Pathophysiology of obesity

A comprehensive review of obesity pathophysiology and its sequelae is beyond the remit of this thesis. There are, however, some fundamental concepts, and important new findings in obesity, that must be addressed before focusing on the specific aspect of obesity pathophysiology that this study intends to research.

Figure 1: Overview of energy balance (used with permission from University of Liverpool School of Psychology department)



In essence, the weight of an individual is dependent on their energy balance. Energy balance is the long term balance between energy intake (EI) and energy expenditure (EE)(85). This is summarised above in figure 1. There are numerous factors that contribute to each. Energy intake is controlled in part by the central nervous system (CNS). The CNS has control over feeding behaviour, and over the neuroendocrine system, which has both short and long term effects. In the short term, release of factors such as cholecystokinin and a myriad of other factors cause the feeling of satiation; a crucial factor in one's portion size. More long-term neuroendocrine factors such as leptin (explained in detail below) are released in levels correlated to the body's fat storage(85). There are a multitude of other central neural circuits that help control energy intake. Neuropeptide Y causes markedly increased appetite whilst the central melanocortin pathway can have a huge number of influences on energy intake. A comprehensive review of such pathways is beyond the remit of this thesis(85). The effect of single gene defects (as discussed below) on these aforementioned systems, and others, can alter energy intake. It must be noted that there is currently great focus on the genetic aspects of obesity. It has been argued, however, that these cannot be the main cause of the obesity epidemic, with significant changes in human genetic makeup unlikely to have occurred in the last two decades(86). Diet is another large factor in energy intake. There is an argument that increases in readily available, cheap, high fat foods, which are highly palatable foods and often in large portions, have had huge influence on the increasing prevalence of obesity(87-89). Factors that effect energy expenditure include exercise levels, purported to be lower in modern society(59, 90). Furthermore, thermogenesis is crucial to energy expenditure. There are two areas of focus in thermogenesis. Firstly, there is much study of the neural pathways that control thermogenesis, i.e. the autonomic system. Secondly, there has been a focus on the area of thermogenesis at the cellular level(85). Beyond these conceptual large umbrella areas of energy intake and expenditure, there are a plethora of other factors that have an influence on weight, such as intra uterine pathologies, birth weight, ethnic origin, sleep and endocrine disorders, amongst others(59). Some factors have an effect on both energy intake and energy expenditure; for example socioeconomic status(59).

One theory regarding weight gain is that susceptibility to weight gain is associated with behavioural risk factors. There are behavioural risk factors for both energy intake and energy expenditure. Whilst behaviour controls a proportion of energy expenditure, it has been argued that it has a greater role in energy intake(91). This concept of behaviour affecting energy intake will be focused on in chapter 1.3.

As aforementioned, a comprehensive review of factors influencing obesity is beyond the scope of this thesis. Certain aspects relevant to this thesis will now be focused on. There have been important genetic discoveries related to obesity in the past decade. The chance of an individual becoming obese when they have an obese relative is estimated to be between 30 -70%(92). The discovery of obese related genes is potentially the most fruitful avenue for successful treatment of this worldwide health concern. There can be no doubt that genetics are crucial to an individual's susceptibility to becoming obese. Hitherto no gene has been discovered to be the sole "obese gene". Unsurprisingly, it is more likely that there is a multifactorial interaction of many polymorphic gene products that are the key to the pathophysiology of obesity(92). Neuropeptide Y and uncoupling proteins are amongst a number of aberrant gene encoding factors that have been implicated in the aforementioned pathophysiology(93).

There are, however, a number of monogenic gene variants that can cause profound obesity, congenital leptin deficiency to name but one. Leptin is usually secreted in adipocytes in the regulation of satiety. In congenital leptin deficiency, where no serum leptin is detectable, hyperphagia and early onset of obesity are caused. Whilst, from a population perspective, the profound effects of a monogenic deficiency is fascinating, for the majority of obese cases, obesity is due to the small, but appreciable, effect of multiple genes and to a greater extent, the individual's relationship with their environment(93). Recently the fat mass and obesity related gene (FTO) was discovered(94, 95). On average, individuals who possess this gene weigh 3 kg more than those with low risk alleles. Recent work has shown that FTO exerts its influence phenotypically by affecting the person's appetite behaviour(96). This is an important finding, highlighting phenotypic effect

being exerted on behaviour, rather than metabolism. There is a great deal of hope that successful treatments for obesity are closer with the important discovery of such genetic developments.

Although the discovery of these genes is crucial to the unravelling of pathophysiology of obesity, it has to be remembered that these genes have been shown to make statistically significant but modest increases in weight, not considerable enough to account for the current obesity epidemic. This leads to the suggestion that the environment and behaviour play a crucial role in obesity(95). It has long been argued that “mechanization is an incontrovertible fact inherent to our social milieu(71)”. Motor transport and white goods (e.g. washing machines) have reduced the possibility of keeping a thermodynamic balance. Furthermore, sedentary leisure activities have replaced a great deal of outdoors activity in children and adolescents alike(71, 87).

The concern with obesity is its end consequences on health. Greater adiposity in children and adolescents leads to greater cardiovascular mortality in adulthood(97). Paediatric obesity can cause polycystic ovarian syndrome, non alcoholic fatty liver disease, a number of cancers and, importantly, metabolic syndrome (hypertension, dyslipidemia, insulin resistance), which occurs in up to 50% of overweight individuals(98). This does not take into account the large social stigma and discrimination obesity carries with it(99).

There can be no doubt that obesity is one of the most important problems in today’s society; its negative ramifications are seemingly endless.

1.2.4 Overview of relationship between migraine and obesity

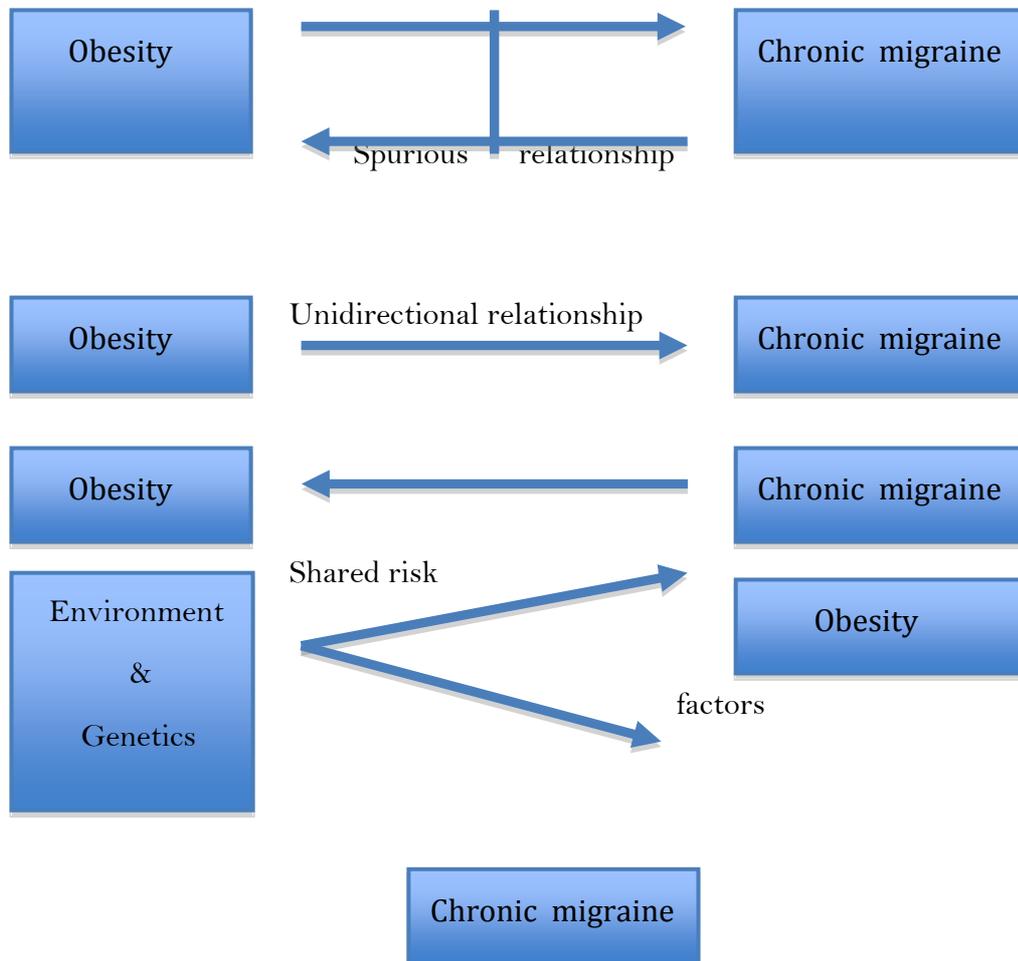
Recently, a relationship between migraine and obesity has been highlighted. A crucial part of the pathophysiology of migraine is the recently developed concept that a proportion of migraine sufferers do not have a static disease, but rather a sub-group have migraine transformation(100). This term means the progression of migraine from low frequency episodic headache leading to

high frequency episodic headache and finally to chronic daily headaches. This transformation may not just be clinical but also physiological, with progression to stroke a possible consequence(101-103). Thus, it has been accepted that it is crucial that risk factors for this form of headache are highlighted to control and remove them and hence ameliorate the potentially devastating effects migraine can have if left to progress. Recently it has been shown that a key risk factor for migraine progression in adults is obesity(100). Crucially, this is a modifiable risk factor, unlike age. One large longitudinal study has shown that overweight or obese adults are more likely to have migraine progression to chronic migraine, after adjusting for co-morbidities and demographics(104). Another cross sectional study suggested a five times greater risk of chronic daily headache in the obese compared to normal weight patient(44). A sub-section of this study suggested that the odds of having frequent headache were 2.9 higher in the obese(44). A third study suggested that obesity is a strong risk factor for chronic migraine headache more than chronic tension type headache(100) and a fourth study suggested that there was a strong association between obesity and headache frequency(105).

All four of these studies were conducted in the adult population and only three studies have been carried out to investigate if the link holds in the paediatric population. The first study found that females had four times the risk of being obese if they suffered from headaches(106). The second found that increased weight was linked to increased headache frequency(107). The third also found a significant correlation between increased weight and increased migraine frequency(108). None of the paediatric studies hitherto have been longitudinal; therefore no direction of association has been elucidated.

There are a number of theories as to how migraine and obesity interact. A unidirectional cause may be part of the pathology, with chronic migraine leading to a more sedentary lifestyle, and migraine prophylaxis often leading to weight gain. Another link is the possible shared genetics between obesity and migraine. This is summarised in figure 2 overleaf.

Figure 2: Previously cited theories on the relationship between migraine and obesity (adapted from published work by Bigal et al(109))



Appetite behaviours are one area of focus by certain obesity researchers. Recent evidence has shown that neurobiological mediators of inter-individual susceptibility to obesity act via appetite behaviour (94, 96, 110, 111). Willer et al have recently reported that the common genes involved in obesity are expressed in the central nervous system(111). The FTO single nucleotide polymorphism is expressed in the hypothalamus, which controls the behavioural aspects of appetite(110). FTO does not cause increased energy expenditure, further supporting the theory that FTO association with increases in BMI are mediated by appetite behaviour.

Recently, Wardle and colleagues highlighted specific eating behaviour using psychometric tools (the Children's Dutch Eating Behaviour Questionnaire (CEBQ)). In particular, focus was placed on satiety responsiveness and external eating/enjoyment of food. Furthermore, using the CEBQ measure, Wardle and Carnell identified that certain eating behaviours are associated with 'adiposity', a state whereby patients are on the trajectory toward obesity(112). With important discoveries like the FTO gene, researchers are interested in the functional expression of such genes(96) i.e. the behaviour of an individual.

Behavioural risk factors for energy intake include patterns of eating and preferences for specific types of foods. It has been previously argued that these behavioural risk factors are "regarded as biological dispositions which create a vulnerability for weight gain and which manifest themselves through behavioural acts(113)".

Work in appetite behaviour is suggesting that aberrant appetite behaviours can be associated (along with a myriad of other factors) with the onset of obesity and research into this is of paramount importance. If one learns how to interrupt this pattern of eating they can potentially arrest the progression to obesity.

Reflecting on the increasing interest in appetite behaviours and referring to the neurobiological chapter 1.4 later in this thesis, it seems entirely plausible that certain neuropeptides, present in both migraine and obesity, are biological dispositions, which create vulnerability for weight gain, potentially mediated by appetite behaviours. This is an argument for why migraine severity should be correlated with appetite behaviours. Plausibly, using the aforementioned theory, the more severe the migraine, the more severe the biological disposition to weight gain through behavioural acts.

This study aims to focus on appetite behaviours in migraine patients. The relationship between migraine and obesity has been highlighted. But the direction of effect, and the underlying relationship is not clear. Theoretically, aberrant appetite may occur in migraineurs that lead to subsequent obesity.

1:2:5 Reflection upon alternative mechanisms in the relationship between migraine and obesity

On reflection of the energy balance (figure 1) section earlier in this section, there are other mechanisms in which migraine could be associated with obesity. Regarding the energy expenditure side of the energy balance, it could be argued that migraine patients have a lower basal metabolic rate. Therefore a lower basal metabolic rate in this group would increase the chance of obesity. From a literature search there is no current work into this area to support this postulation in the migraine population.

Alternatively, it could be argued that migraine patients expend less energy, putting them at higher risk of obesity. Research has shown that exercise can precipitate an migraine attack in a proportion of migraine patients(114). There is work suggesting that almost half of migraine sufferers experience exertional exacerbation of headache(115). It could, therefore, be argued that certain migraine patients avoid exercise for fear of an attack. This adaptive behaviour would put them at increased risk of obesity. However, contrastingly, there is also evidence that regular exercise reduces migraine frequency and severity(116-119). Of course it is still plausible that due to the general perception that exercise exacerbates migraine, migraineurs avoid exercise, in spite of its supposed benefits.

Similarly, research has shown that over 80% of chronic migraineurs suffer from fatigue(120). This fatigue could potentially reduce a persons desire and/or ability to exercise, again putting them at increased risk of becoming obese. The only current study addressing exercise levels in the paediatric migraine population found that migraineurs do more exercise than their migraine free peers(121). It is clear that exercise in paediatric migraineurs has not been thoroughly studied. It must also be noted, however, that in a recent study, the basic paradigm that physical inactivity causes obesity has been called into question. In a longitudinal study of a general paediatric population it was found that physical activity was not predictive of changes

in body fat percentage(122). Conversely, body fat percentage was predictive of changes in physical activity. Essentially, this is the reverse causality of the generally accepted concept that physical inactivity leads to obesity. This is an important finding that challenges this idea that minimal exercise, a large facet of energy expenditure, is integral to weight gain. This re-directs the focus upon the energy intake side of the energy balance. This is strong support into the justification of a novel study addressing appetite behaviours, one aspect of energy intake. That being said, further work is needed in this area before firm conclusions can be made. It is still plausible that the relationship between migraine and obesity is mediated by a reduced energy expenditure due to poor exercise levels. This is potentially as likely as the relationship between migraine and obesity being mediated by appetite behaviour on the energy intake side of the energy balance (Figure 1). Further study would be entirely worthwhile to research the effect exercise patterns have on the relationship between migraine and obesity.

Chapter 1:3 What are appetite behaviours?

1.3.1 Appetite Behaviour

The review of obesity highlights that it is a global issue that has great impact on health. The strong influence of genetics on this condition is incontrovertible, however, the high increase in obesity levels over the last twenty years suggests other key factors are involved in the disease. The 'obesogenic environment' is well cited in the literature as having a large role in recent obesity levels. Increasingly sedentary lifestyles, associated with readily available and widely advertised high fat, high sugar and energy dense foods at affordable prices are a huge part of the environmental influence. One analogy has proposed that 'genes load the gun, but the environment pulls the trigger'(123).

One issue with the current crisis of obesity is the fact that there remains such a great deal of variation in the population exposed to the same 'obesogenic environment'. One theory is that there is an inter-individual susceptibility to obesity that is, at least in part, mediated by variation in appetite behaviours(88, 110).

Aberrant appetite behaviours are when an individual's appetitive traits increase their susceptibility to obesity in their environment(112). A simple example is if an individual has poor satiety responsiveness, whereby an individual responds poorly to their internal satiety signals and therefore eats a greater amount of food(124, 125). There are many psychological theories of appetite behaviour surrounding food cravings that are triggers for overeating. The appetite behaviours literature is extensive. It must be noted that all aberrant appetite behaviours do not occur exclusively in the obese; they can also occur in people of normal weight; for example binge eating, exhibited in bulimia nervosa, does not necessarily mean a person will be overweight.

One theory hypothesises external eating as a key aberrant eating behaviour. It suggests that certain people are more sensitive to external food cues than others and eat in response to those environmental stimuli, irrespective of their internal signals of hunger or satiety. It is suggested that favourable environmental cues, such as smells or signs, can cause large food cravings and drives for food even when fully satiated(126).

An overlapping concept to this is the idea of food cue responsiveness. Greater food cue responsiveness can mean all manner of things. It can mean responding more to highly palatable appearing foods, responding to foods physically visible or responding to time cues e.g. 'lunch time' rather than satiety cues(127). The hypothesis of eating in the absence of hunger in response to food cues has been shown in the paediatric population(128). Food cues are often measured in ingestive laboratories. They are considered demonstrable, observable appetite behaviours. For example, ten minutes after eating to satiation in an ingestive laboratory setting, children were left in a room with highly palatable looking foods (chocolate, crisps, sweets) and obese children were shown to override their satiety signals to a greater degree than lean controls, exhibited by the obese subjects eating more food(128). Note the similarity between the two appetite behaviour theories of external eating and food cue responsiveness; both propose that certain people respond to the physical presence of foods, in particular, attractive, highly palatable appearing foods.

A more recent theory, a component of the theory of "the power of food(129)" focuses on the effect that the presence of food has on appetite(129). This concept overlaps with the idea that the proximity of food physically alters the person's relationship with that food. In other words, if the food were available, but not directly in front of them, they would act differently i.e. not search out the food to eat. A subtle difference of this concept from the former two, is that it is trying to assess the effect that living in a food abundant environment has on appetite, rather than assessing if someone overeats in this environment(129). The theory of the power of food can be seen to be the flip side of food cravings (mentioned in detail below). Power of food is

focusing specifically on the effect of food in close proximity on a person's relationship with food. Conversely, food cravings highlight a person's cravings for a specific food, in the absence of that food.

One more component of the theory of the power of food is food availability. This is associated with the current abundance of food to which much of the developed world is exposed. It has been postulated that because there is such wide spread availability of food, not necessarily in close proximity, but easily accessible, that this alters a person's appetite behaviour(129).

Another concept is that of the restrained eating theory. This theory suggests that dieting can cause excessive weight through bingeing. People who diet suppress their feeling of hunger cognitively and eat less. These cognitions are undermined (disinhibition), however, with high food cravings causing disinhibition and binge eating, restrained eaters are more likely to overeat than non dieting individuals; known as 'counter – regulation'(130). Recently, this theory has been developed in another tool(131), which splits restraint eating behaviour into rigid and flexible cognitive restraint. Rigid cognitive restraint is where an individual has an all or nothing approach to eating food, and when trying to reduce food intake does so in a strict and meticulous fashion. It is this rigid approach most likely to result in diet breakdown(131).

Emotional eating is another theory of appetite behaviour; it suggests that some people eat in response to their emotions, not to internal signals such as feelings of hunger or satiety. In the case of emotional arousal or stress, strong food cravings cause emotional eaters to respond by eating excessively(132).

Emotional eating, and external/food cue responsiveness/food presence are arguably associated with a recent, distinct, and evolving concept in appetite; that of hedonics (discussed below) in eating. The link of emotional eating with hedonics is that emotional eaters are purported to be stimulated to eat due to low self-esteem, thus it could be suggested that, in seeking food, they are seeking pleasure from eating palatable foods(133, 134). The link of external eating with hedonics is that arguably visible foods are only so attractive and desirable if they offer some satisfaction or pleasure(134).

1.3.2 Hedonic versus Homeostatic mechanisms of appetite

There is evidence that certain groups of patients have a heightened hedonic response to food, i.e. a hyper-responsiveness to the sensory properties of food. It has been previously shown that these hedonic drives can override physiological satiety signals (135). Put simply, people can eat high density, highly palatable foods when they feel full. A study previously showed that when participants had to rate the pleasantness of the high fat food they were eating, those who rated the food highest had the greatest adiposity. The more overweight the participant, the more they enjoyed the food (136).

A crucial emerging behavioural neuroscientific concept is that of 'liking' and 'wanting' that mediate physiological processes. Liking is suggested to be simply the hedonic response of a stimulus(134). The hedonic response is the brain's reaction to a pleasurable sensory stimulus. A simple example is the enjoyment/pleasure experienced whilst eating a sweet. In contrast, wanting is the behavioural incentive aspect of the same stimulus. To be clear, wanting is not the hedonic response to the stimulus. Rather, it is the drive or pursuit of a stimulus(134). Hedonic drive is a new theory that contests the classic concept of homeostatic drive. Homeostatic drive is the concept that there is a stable internal state. That there is a set point that is regulated whereby maintaining a stable physiological state. When reflecting upon appetite, this may well be seen to support the homeostatic theory, because the body should theoretically have a plethora of set points for nutrients and deviation from these leads to hunger and, of course, when nutrients are sufficiently ingested satiation occurs(134). Conversely, a criticism of this theory is that there is unlikely to be set points for hunger, but rather likely more fluid 'settling points' that are influenced not just by internal satiety signals but external factors such as availability and palatability of food and also the eating behaviours of the individual(137).

The hedonic concept transcends simple regulatory set points, and rather suggests there are motivational behavioural drives created in the brain for

stimuli. The arguments of the need for research into fresh behavioural concepts and the shortcomings of the classic homeostatic regulation concept are beyond the remit of this thesis. Safe to say, the hedonic behavioural concept is evolving with pace. When this is applied to appetite, wanting can manifest as cravings for particular food types. These are often highly palatable, high calorie, highly pleasurable foods; thus food cravings have a role in the concept of hedonic physiological drive rather than homeostatic physiological drives(138). It should be noted, however, that hedonic and homeostatic mechanisms are not mutually exclusive when referring to appetite. The high palatability of food can produce a hedonic response which delays the onset of satiety(134). It will, therefore, be important to map out food cravings in this study, in order to address the particular ‘wanting’ or, food cravings of migraine patients. Food cravings have informally been studied in migraineurs, but not in the context of rigorous appetite behaviour, and will be reviewed in a later section(1.3.5).

Other concepts overlap with the umbrella term of hedonics in appetite. Firstly, food reward(139), a less well-researched appetite behaviour in the paediatric population, overlaps with hedonic appetite. The hypothesis suggests that obese individuals experience a greater subjective reward from consuming highly palatable, high-energy foods(127). It has been shown, in an ingestive laboratory setting, that obese individuals will work for longer on a computer task to gain a palatable reward than lean individuals(140). Thus food reward suggests that if obese individuals work harder for these rewards, this is potentially because they experience greater reward, presumably through enjoyment or pleasure of eating, be it the sensory aspect or another aspect. Secondly, another power of food concept is that of ‘food tasted’(129). This focuses on how certain people focus on the pleasure and enjoyment of the food they eat(129). Thus hedonics can be seen to encompass these two concepts.

Another area linked to hedonics, and even to food cravings, is food preferences(141). Essentially the premise of this concept is that people have preferences for high-density foods (fats) as opposed to low-density foods (fruit and vegetables). This can also be seen to be linked to the hedonics of

appetite. It has been shown that overweight adults have higher energy density diets than people of normal weight (142). Hitherto, the liking and wanting of high density foods in this group have not been comprehensively shown(127). It would, however, presumably follow that those who have food cravings for highly palatable foods are those most likely to eat such foods.

Another important appetite behaviour is satiety responsiveness. This is essentially how an individual responds to internal satiety signals. In the adult literature it has been shown that obese patients have a lower satiety responsiveness compared to lean controls(124). Similarly, in an adolescent population, in an ingestive laboratory setting, obese children did not exhibit any downward regulation of their intake to a test meal, offered immediately after a preload meal, compared to lean controls(125). This is but one example of how children with greater adiposity show weak satiety responsiveness, whereas, strong satiety responsiveness is based on the theory that an individual who is responsive to his/her internal satiety signals will reduce food/energy intake in response to their preload intake(112). The normal adaptation to reduce intake after an energy dense preload has been coined 'energy compensation(127)'. In addition to energy compensation, another suggested good indicator of satiety responsiveness is eating rate. It is presumed that if an individual's eating rate slows it is a response to internal satiety signals(139). Once more in the elder paediatric population, in an ingestive laboratory setting, it was shown that obese children continue to eat at the same rate compared to lean controls(143).

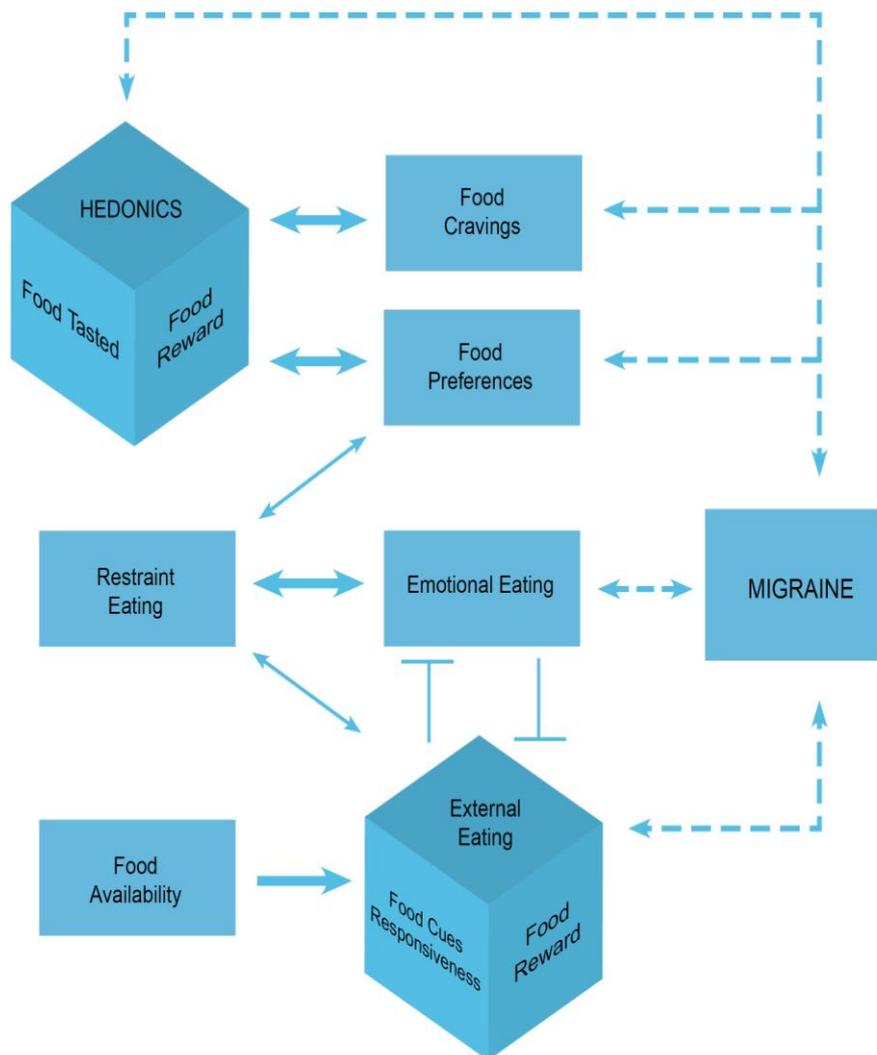
It is clear to see there is a plethora of different concepts, theories and theorists regarding appetite behaviour. It is important to highlight that certain appetite behaviours have been linked to the inter-individual variability of response to environmental cues causing a variation in risk of weight gain(126). Thus one plausible mechanism for the variation of weight is the individual variation of appetite behaviour expression in the population.

It has recently been shown that children's appetite behaviours are consistent over time(144). Striking continuity was shown in a prospective study of over four hundred children analysing seven different subscales of their appetite

behaviour over eight years. This is a crucial finding for this proposed research. This study hypothesises, as aforementioned, that severe migraine leads to aberrant appetite behaviour, which, in turn, leads to increased adiposity. Thus, by capturing children at migraine diagnosis, the study hopes to elucidate whether children at the severe end of the migraine spectrum, will have the poorest/most aberrant appetite behaviour, which puts them at highest risk for increased adiposity. The finding that children's appetite behaviours are consistent further supports the plausibility of the hypothesis that poor appetite behaviours are strikingly consistent through childhood into adulthood.

Overleaf is a schematic overview (Figure 3) of all the discussed appetite behaviours. The solid arrows represent the close associations already discussed between certain appetite behaviours. The 3-D blocks represent distinct appetite behaviours on each face that has theoretical overlaps with one another. The dotted lines are hypothetical associations between migraine and the different appetite behaviours, which the study aims to identify.

Figure 3: Overview of interrelationships between appetite behaviours and their potential relationship with migraine



1.3.3 Aspects of appetite that have already been studied in migraineurs

1.3.4 Dietary triggers of migraine

By far the most widely documented component of diet in migraine is the discussion of foodstuffs that trigger migraine. It has long been suggested that certain foods precipitate the onset of a migraine. Although not strictly relevant to this study, it is the largest volume of literature on diet in migraine. It is very common for migraine patients to avoid certain foods based on what they have been told from varying sources of differing rigor. This behaviour is undoubtedly related to the appetite behaviour aspect of the proposed study.

High levels of caffeine ingestion (often caffeinated soft drinks are consumed by children) with subsequent sudden abstinence can cause withdrawal headache and exacerbation of migraine can ensue. The pathophysiology of this trigger is that caffeine intake causes vasoconstriction and a rebound vasodilatation and there can be an increase in blood flow when caffeine intake is arrested(145).

Cheese is commonly suggested to be a food trigger, due to the high concentration of tyramine it contains(146). The high levels of tyramine cause a vasoconstriction secondary to noradrenaline release(147).

Chocolate is another foodstuff that can trigger migraine. A number of ingredients could be the trigger (Refer to table 1 below). Again, any of these substances could precipitate headache by alteration of cerebral blood flow and/or release of noradrenaline(148).

Alcoholic drinks are a possible substance to trigger migraine (refer to table 1) in adolescents. The pathways in which these chemicals induce a migraine are multiple: amongst others tyramine, as aforementioned, releases noradrenaline and histamine releasing nitric oxide from the vascular endothelium(146, 149).

A discussion of the less well-described food triggers is beyond the remit of this thesis, but note table 1. Amongst other triggers, nitrites, in a lot of cured meats, have been cited as causing migraine, theoretically by nitrites acting on the endothelium causing vasodilatation(148). Monosodium glutamate can induce migraine in a very small proportion of migraineurs. Aspartame, frequently used as a sugar replacement, has been associated with triggering headaches, as have fatty foods(146).

Irrespective of whether dietary advice has been given at a primary care level, or simply colloquial advice, dietary triggers are well known by migraine patients; they are commonly discussed in migraine clinics as part of optimal management.

Food neophobia is defined as the rejection of foods unknown to the child (150). In contrast, food avoidance is avoiding a great deal of known or unknown foods resulting in a habitual diet characterized by a low variety of foods. Whilst the former is an inherent adaptive human trait, the latter is an aberrant behaviour(150). Great deals of dietary triggers are known in migraine, and patients cite a great deal more. It will be important to elicit within appetite behaviours if there are any particular foodstuffs that patients avoid, and whether they have reasons for doing so, such as known triggers or allergy, or advice from a health care worker or layperson. If certain foods are avoided this needs to be highlighted in results. Certain avoidance, whether founded or not, will have an influence on appetite behaviours and it is essential this is duly considered.

Table 1: Dietary triggers in migraine(146):

Food type	Theoretical chemical trigger of migraine
Cheese	Tyramine
Chocolate	Phenylethylamine, Theobromine
Citrus fruits,	Phenolic amines, Octopamine
Meats (hams/Cured meat)	Nitrites, Nitric oxide
Dairy products	Allergenic proteins (casein etc)
Fatty foods	Linoleic and oleic fatty acids
Snack foods, Eastern foods	Monosodium glutamate
Coffee, tea, coke	Caffeine withdrawal
Food dye additives	Tartrazine, Sulfites
Artificial sweetener	Aspartame
Alcoholic drinks (wine, beer)	Histamine, tyramine sulfites
Fasting	Stress hormone release, hypoglycaemia

Table one is a summary of the established triggers of migraine and the theoretical chemicals within each substance that is thought to be the cause of the trigger,

1.3.5 Food Cravings in migraine

Blau (151) informally recorded the eating patterns of migraine patients around the time of their migraine attacks. He highlighted that a subset had substantial cravings for certain foods. In particular, a pattern of cravings for starchy, carbohydrate based foods was classic (151). The methodology of this study was very informal, with researchers simply directly asking the participants if they could eat around the height of their headache, and if so, what foods they ate, if they had any specific cravings, and if they had any accompanying nausea.

In another study by Dalton, whilst trying to highlight specific triggers for spontaneous migraine attacks, it was found that 67% of patients had fasted in the previous twenty four hours. These two studies highlight that there may be a role for appetite behaviour in the pathophysiology of migraine. Both studies focused on issues around the time of attack. The aim of this study is to design and conduct a more formal study focusing on whether trait migraine affects trait appetite behaviours i.e. the day-to-day appetite traits of a migraine sufferer, not their appetite around attack.

1.3.6. Migraine medication and appetite

It is well documented that certain migraine medications cause alteration of body weight. Pizotifen causes weight gain in children, irrespective of their previous weight and irrespective of the dose(152). It has been suggested this is due to the role of the serotonergic system on appetite. Conversely, Topiramate treatment causes substantial weight loss(56), irrespective of previous BMI. These side effects are important, impacting on clinical management. For example, changes in appetite and weight can lead to poor compliance and discontinuation of pharmacological therapy. Ingestion laboratories or psychometric tools have not formally studied the mechanisms of medication related weight change hitherto.

The aim of this study is to identify the pattern of appetite behaviours in children with migraine. The study will focus on the children's stable eating behaviours, i.e. their eating behaviour "traits" between acute attacks(151). The aim of the study is to focus on this rather than their appetite behaviours around the time of attacks, i.e. the "state" appetite behaviours. Eating behaviour around the time of migraine attacks has received attention in previous studies with patients reporting specific cravings (e.g. chocolate and carbohydrates) prior to the onset of an aura of migraine, although standardized measures were not used(151). Blau et al showed that missing meals could induce an acute attack in migraineurs(153). Both migraine and obesity are stable traits i.e. chronic conditions, therefore this study will focus on the trait eating behaviours since the intention is to identify chronic eating behaviours which, in other literature, has been associated with increased adiposity(132).

Patients with migraine were studied to see if they had eating disorders and 88% of the female population did have eating disorder. This is much higher than the general population. Of importance, the majority (56%) stated migraine had preceded the onset of their eating disorder. This is crucial in suggesting that migraine causes aberrant appetite behaviours, irrespective of their subsequent clinical manifestations. These patients are supposedly under-eating as a result of migraine rather than over-eating. This begs the question whether the relationship between migraine and appetite occurs at both ends of the appetite spectrum. Can migraine cause aberrant under eating as well as overeating? Is there a non-linear association to this potential relationship?

1:3:7 Other chronic pain syndromes and appetite

In stark contrast to this study's hypothesis, a study of chronic pain in an elderly population highlighted a self-reported appetite impairment(154). This suggests that chronic pain, be it migraine or another pathology, actually leads to reduction in appetite, the opposite of this study's hypothesis. Whilst this is worth note and consideration, the author of these findings suggests much greater work is needed to establish any casual relationship between chronic pain and diminished appetite. Furthermore, the population is at the other end of the age spectrum, so not strictly transferable to this planned study. A further study of children and adolescents with chronic pain (caused by a wide spectrum of pathology) showed that 51.1% had problems attributed to eating. This suggests that chronic pain may cause an appetite reduction in child sufferers, contrary to this study's hypothesis. Furthermore, the majority of participants that reported appetite loss were migraine participants. At this point, a conceptually important distinction has to be made. On first considering this result it appears to completely contradict this study's hypothesis, however, appetite loss around the time of migraine attacks, as is reported in this study(155), is well cited. Over 82% of migraine sufferers have been shown to be anorexic around the time of attack(156). Thus, in this light, these findings are somewhat unsurprising. This study's hypothesis is focused on migraineurs trait appetite behaviours, i.e. their chronic appetite behaviour, outside of attacks. The aforementioned study,

although focusing on chronic pain, is reporting migraine sufferers' appetite behaviour around the time of attack. Recent work on rats has shown that appetite is maintained in the face of chronic pain. The study highlighted, that, when being stimulated with sustained noxious stimuli appetite did not alter(157).

Chapter 1:4 The neuropeptides that underpin the neurobiology of migraine, appetite and obesity:

It is important at this point to review the neurobiology that underpins the plausibility of the relationship between migraine, appetite and obesity.

Chapter 1:4:1 Calcitonin Gene Related Peptide

Calcitonin gene related peptide (CGRP) has been shown to be a key link between migraine and obesity, with levels being higher in both pathologies. CGRP(158) is a 37 amino acid neuropeptide, which was discovered twenty years ago. There are two forms of CGRP, α CGRP and β CGRP; varying by only three amino acids, they have identical effects biologically on vasculature(159). CGRP possess a wide number of functions within the central and peripheral nervous system(160). Importantly, CGRP is synthesized and stored in the trigeminal ganglion neurons(161). It can be released when trigeminal ganglion neurons are stimulated(162), which, crucially, causes potent vasodilatation of the cranial blood vessels(160). It has been shown that CGRP is implicit in the pathophysiology of the onset of migraine(163). Studies have shown that CGRP levels are elevated during a migraine attack(164, 165).

Moreover, it has been shown that an infusion of CGRP induces a migraine attack in migraineurs(163). Furthermore, arguably the most important experimental data linking CGRP to migraine, is two extensive RCT's that successfully trialled CGRP antagonists to reduce migraine severity(166). Two pharmacological CGRP antagonist agents reduced migraine attacks significantly. Firstly, the CGRP antagonist BIBN 4096 BS was shown to significantly reduce migraine severity at 2 hours and at 24 hours compared to placebo(26). More recently, the CGRP antagonist MK – 0974 was shown to significantly reduce migraine pain at 2 hours compared to placebo. CRGP is instrumental in migraine pathology.

Plasma CGRP is elevated in obese patients(109). A study nearly two decades ago suggested that CGRP is intrinsically related to obesity in the female population(167). Rat studies show that CGRP is raised in the obese subjects prior to onset of obesity and becomes more elevated once obese(168).

Thus, CGRP is a crucial neuropeptide in the theoretical framework for how migraine, appetite behaviour and obesity interrelate. It is clear CGRP is key in the underpinning of migraine pathology. It has been shown that CGRP is elevated in obese subjects, even before the onset of obesity. It fits in, therefore, with the theory suggested by Bigal et al(109) that migraine may be involved in the progression to obesity, as CRGP is elevated in migraineurs and is raised just prior to the onset of obesity, leading to its onset. Therefore migraineurs, with their higher levels of CGRP may increase the risk of obesity onset. The chronic rise in CGRP mediator can then lead to increased frequency and severity of migraine(109). The intermediary steps between migraine and obesity and severity of migraine remain unclear. Irrespective of the neurobiological mechanisms, appetite traits are a physically demonstrable behaviour that could plausibly have a role in leading to obesity. These need greater focus, not least because this is the area that, from a preventative viewpoint, will need to be addressed.

Chapter 1:4:2 OB Protein (Leptin)

OB protein, commonly known as 'leptin', is the product of the OB gene. The discovery of a mutation of the OB protein was a tour de force in the mid-nineties(169). It was shown to cause hyperphagia in mice. Leptin is a polypeptide hormone secreted by adipocytes. Since the discovery of leptin, a plethora of work has shown that leptin undoubtedly has a role in appetite control(170). It has a multitude of roles; it is involved in regulation of feeding behaviour, metabolism and the autonomic nervous system(109, 170).

Exactly how leptin interfaces with weight regulation remains unclear. Leptin levels certainly correlate with current levels of adiposity. The higher the level of fat deposition, the higher the concentration of leptin(171). It was first postulated that OB protein reduced food intake and increased energy

expenditure(172), hence it was named leptin; derived from leptos – Greek for thinness. It was shown that leptin directly acts upon OB protein receptors at the hypothalamus(173), thus a direct role in satiety seemed logical. High levels of leptin do not invariably reduce appetite or obesity, however(170). This suggests that there is potential leptin insensitivity at the level of the brain receptor, or alternatively, there may be a post receptor defect in CNS communication to appetite centres. This ambiguity demonstrates that leptin's role in appetite is unclear.

Low leptin levels are linked to a high risk for the onset of obesity(170). With regards to the proposed research, this is an interesting finding. It has been suggested leptin is involved in food seeking behaviour, the inner drive for foods, rather than satiety mechanisms. Thus, if leptin levels are low, a high food drive ensues and ravenous food seeking behaviour occurs, resulting in hyperphagia(170).

This concept of leptin being implicated in food seeking behaviour is important to the neurobiological justification of this study. A recent case control study showed that leptin levels were significantly lower in migraine patients compared to healthy matches(174).

Leptin is one of the key neuropeptides that justify this study's hypothesis. The migraine study above highlights that migraineurs have low leptin; therefore one mechanism in which migraine is a risk factor for obesity is by low leptin level mediation, as it can lead to aberrant hyperphagic food seeking behaviours.

Leptin further highlights the biological overlap between migraine, appetite behaviour and obesity. When administered acutely, leptin causes vasodilatation and also has inflammatory properties. Both are well documented to have a large role in migraine pathophysiology(174).

Chapter 1:4:3: Orexins/Hypocretin

Orexins are another class of neuropeptide, previously named hypocretin. The two types, Orexin A and Orexin B, are very similar molecules; they both interact with two receptors: orexin receptor 1 (OX1) and orexin receptor 2 (OX2)(175). Subsequent to the confirmation that hypocretin has a role in ingestive behaviours, it was renamed “orexin”, which derives from the Greek word Orexis(176), meaning appetite. It was shown that administration of orexin to rats increased appetite and delayed the onset of satiety(177). Furthermore, administration of an orexin one-receptor antagonist reverses the norm, reducing appetite and hastening satiety(178). It was initially thought that orexins were focused on the lateral hypothalamus(179). It has since been established that orexin is involved throughout the CNS and its roles are diverse. Amongst other roles, it is integral in sleep/wakefulness patterns and the autonomic nervous system(180).

With relevance to the prospective study, it is important that orexins have been shown incontrovertibly to be involved in regulation of appetite behaviour. They are involved in satiety signalling and are shown to increase food intake by prolonged feeding behaviour(176).

There has been much research of orexin’s role as an analgesic. Previous work has “shown strong evidence for a role for orexin in the modulation of nociceptive processing(181)”. In both mouse and rat studies orexin A had clear anti nociceptive properties. These findings have relevance to migraine. Currently, the role of orexins in migraine has barely been investigated. However, a recent study by Sarchielli et al showed migraine patients had statistically significant higher levels of orexin in their CSF compared to controls(182). The authors of this study suggest that these results should be interpreted as a neurobiological “compensatory response to chronic pain(182)”. In other words, there is an altered expression of orexin from the hypothalamus in response to chronic stress (due to chronic pain).

Thus, in keeping with the hypothesis, this previous work all supports this study’s hypothesis. If migraine causes a chronic stress on the hypothalamus,

this leads to increased levels of orexins, which subsequently can alter eating behaviours, causing increased food intake due to altered satiety signals, eventually leading to the onset of obesity.

Hitherto, no direct studies have been conducted trying to link migraine and obesity using orexins as a common pathway(183).

In an alternative concept, Bigal et al(109) postulated an indirect link between orexin and migraine. Low CSF orexin levels are found in the vast majority of narcoleptic patients, and migraine pathology has a higher prevalence in narcoleptic patients than in the general population. The biological hypothesis behind this being that low orexins cause a vasodilatation(109). Without formal study this concept is merely speculative. Nevertheless, it is clear to see orexin as an important neuropeptide that needs further investigation in migraine, and has a clear biological plausibility in this study.

Chapter 1:4:4 Serotonin

5-Hydroxytryptamine, or Serotonin (5-HT), is synthesized from the amino acid tryptophan by the enzyme tryptophan hydroxylase (TPH) into 5-Hydroxytryptophan that is then decarboxylated by the aromatic L-amino acid decarboxylase (AADC) into 5-HT(184). The second of the two isoforms of TPH, TPH2, is brain specific and is expressed exclusively within the raphe nucleus, which lies in the brainstem. The serotonergic system from the raphe nucleus has persuasively been implicated in migraine pathophysiology. It is important to note that, whilst this is true, there is conflicting data in the literature. Irrefutable conclusions have not been reached(185).

There are a number of trends that have been elucidated. Firstly, and most importantly regarding this research study, serotonin levels have been demonstrated to be lower in migraine sufferers than non-migraine patients interictally. Furthermore, 5-hydroxyindoleacetic (5-HIAA), a metabolite of serotonin, is higher interictally in migraineurs than in non-migraine patients(186). To further support this, there is increased brain serotonin synthesis in migraine patients(187). 5-HIAA concentrations are increased in the cerebrospinal fluid of migraine patients, suggesting increased breakdown

of serotonin in the central nervous system(188). This work suggests that chronically, migraine is a state of relative serotonin deficiency. This has been further supported by recent neuro-imaging studies, which used 5HTTR ligands and found increased availability in brainstem 5-HTTR in migraine patients. This is consistent with decreased levels of 5-HT at the synaptic cleft, due to decreased synthesis and/or release(189). Lastly, physiological studies have shown that migraineurs, interictally, have increased intensity dependence on the amplitude of auditory and visually evoked potentials, characteristic of low 5-HT transmission(190).

Serotonin has been linked to the state of being satiated. It has a role within meal satiation and also with the end state of post meal satiety(180). In rodent studies it has been shown that administering 5-HT or precursors, such as tryptophan, significantly reduce food intake and eating rate. Moreover, drugs that increase release of 5-HT have been shown to reduce food intake. Examples include selective serotonin reuptake inhibitors such as Fluoxetine(170). Sibutramine, a serotonin and noradrenaline re-uptake inhibitor (SNRI) is also a licensed anti-obesity agent; it is in National Institute For Health and Clinical Excellence (NICE) anti-obesity guidelines, because it is an effective hypophagic drug. Conversely, pharmacological agents such as p-chlorophenylalanine (pCPA) block the synthesis of 5-HT and increase food intake(170). It has been suggested that serotonin has a number of interrelationships with other endogenous peptides involved in satiety, such as corticotrophin releasing factor (CRF), cholecystokinin (CCK) and neuropeptide Y (NPY)(180).

It is clear that serotonin is a pertinent neuropeptide in this study's hypothesis. High levels of serotonin reduce appetite, as shown by rodent and pharmacology studies. Low serotonin, however, causes increased appetite. Migraine is a state of chronic low serotonin. It follows then, that the low serotonin state created by chronic migraine would potentially lead to increased appetite in its sufferers. This is crucial to the plausibility of the planned study.

Table 2: Summary of relevant neuropeptides overlapping in appetite behaviour and migraine(109):

Appetite: ↑ = Increases appetite.

↓ = Decreases appetite

Migraine: ↑ = Increased levels in migraine patients

↓ = Decreased levels in migraine patients

Factor/Hormone	Appetite	Migraine
NPY	↑	↑
Orexin - A	↑	↑
Leptin	↓	↓
Serotonin	↓	↓
CGRP	↑	↑

Chapter 1:5 Aims of MPhil Study

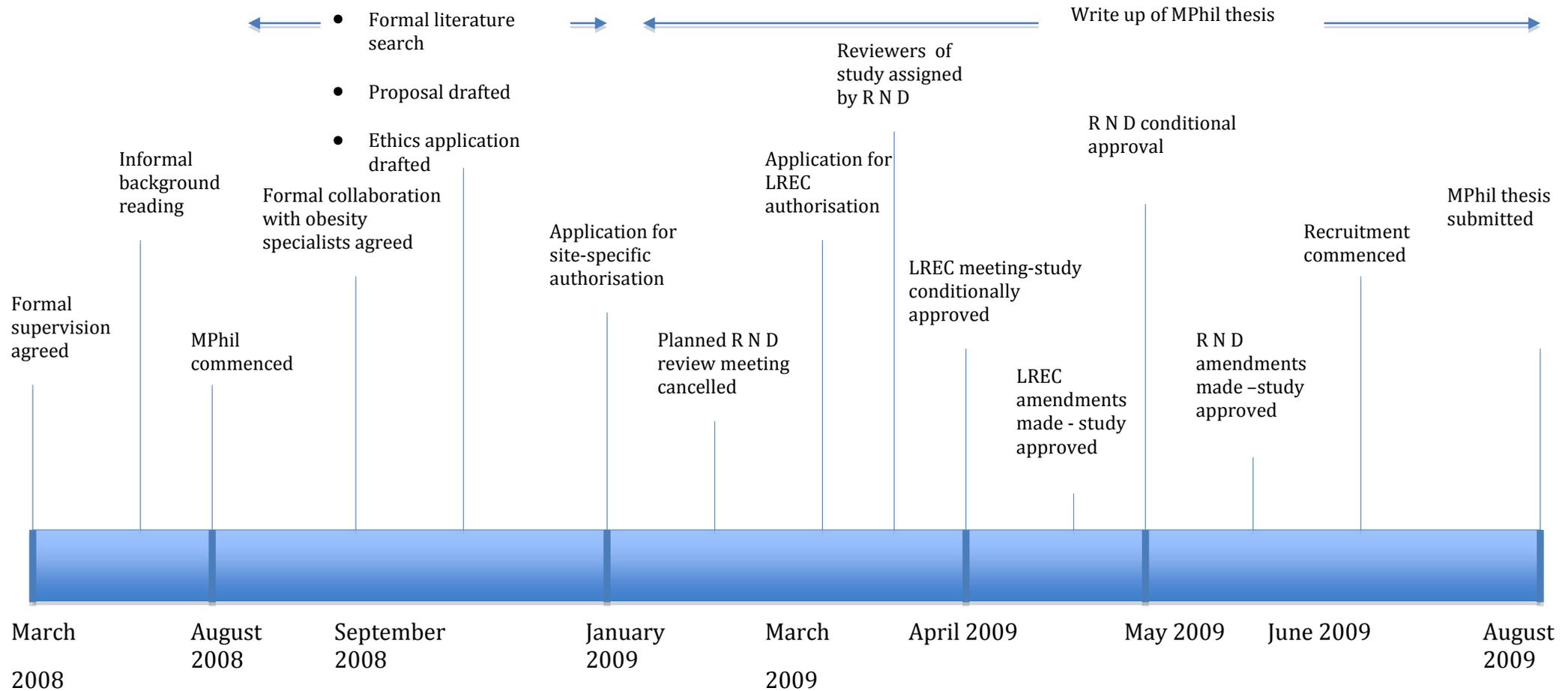
There are three key aims to this MPhil thesis as follows:

1. Firstly to undertake a formal literature review of the relationship between obesity and migraine in both the paediatric and adult population.
2. To design a pilot study to assess the relationship between migraine severity and appetite behaviour.
3. Conduct the pilot study, to address the following questions:
 - a) Feasibility of study design
 - b) Feasibility of participant recruitment
 - c) Utility of psychometric tools in addressing hypothesis
 - d) Elucidate any relationship between increased migraine severity and aberrant appetite behaviour by completion of study.

Hypothesis of pilot study:

The hypothesis tested was that an increase in migraine severity would be associated with an increase in aberrant appetite behaviour.

Chapter 1.6 Timetable of MPhil thesis:



Chapter 2: Methods

2:1 Methodology of formal literature search for previous studies into the area of migraine and obesity:

To assess the current literature systematically a number of formal literature searches were performed in the embryonic stages of the MPhil. Examples of such searches are given below in figure 4 and figure 5. It must be noted that regular literature searches were continued throughout the conduct of the MPhil to ensure new relevant published work was not overlooked.

Figure 4: Example of a search strategy using NHS health information resources:

No	Database	Search term	Hits
1	MEDLINE	migraine.ti,ab	19961
2	MEDLINE	exp MIGRAINE DISORDERS/	19614
3	MEDLINE	obesity.ti,ab	79007
4	MEDLINE	exp OBESITY/ OR exp OBESITY, MORBID/	93835
5	MEDLINE	obesity.ti,ab [Limit to: (Age Groups All Child 0 to 18 years)]	17778
6	MEDLINE	1 AND 2 AND 5 [Limit to: (Age Groups All Child 0 to 18 years)]	15

Figure 5: An example of a search strategy using the University of Liverpool Search Engine:

Search for "Any word=(migraine) And Any word=(obesity) And Any word=(paediatric)" found 1988 results

Database Name	Status	Hits	
MEDLINE (Ovid) - RECOMMENDED	DONE	0	
PsycINFO	DONE	2	View
ScienceDirect	DONE	43	View
Scopus	DONE	1288	View
Web of Knowledge	DONE	115	View
AMED - Allied and Complementary Medicine	DONE	0	
CINAHL	DONE	3	View
Cochrane Library	DONE	1	View
ebrary	DONE	492	View
Intute: Medicine	DONE	0	
Journals@Ovid Full Text	DONE	44	View
Combined Results	First 152 records	1988	View

Chapter 2:2 study design overview:

The proposed study is a pilot, cross-sectional questionnaire based study. Migraine patients will be recruited from the tertiary paediatric clinics at Alder Hey Hospital only.

- Participants will be between 5 and 16 years old, and will include both sexes.
- Participants will be new referrals to Alder Hey neurology department. This is necessary because new referrals will be a proxy for new onset of migraine, or at least an increase in severity and hence a change in the neurobiology of their migraine (and thus a potential change in their appetite behaviour).
- Sample size: After two consultations with a statistician it was decided that a cohort of 90 participants would be appropriate, consisting of 60 migraine and 30 other non-primary headache sufferers. This sample size was calculated by the statistician based on the statistical concept that for every psychometric tool being measured against migraine severity 10-12 participants would be needed to show an effect size. There are 5 psychometric tools being measured against the migraine severity predictor, therefore a sample size of 60 migraine patients was deemed sensible. A control group of 30 was suggested by the statistician; because this was a pilot study and there were no similar studies in the area therefore the statistician decided there was a need for a control arm to the study.
- Participants must be drug naïve, based on the consideration that some migraine medications alter weight (refer to treatment of migraine chapter 1.1.7), and presumably, therefore, appetite behaviour.

Inclusion criteria:

Diagnosis of migraine based on clinical criteria by the treating paediatrician. The International Headache Society Classification developed for adult migraine (see Appendix A) will be used as an adjunct.

Exclusion criteria:

- Under 5 years old
- 17 years of age or over.
- Known presence of a secondary cause of migraine-like headache e.g. brain tumour.

Methodology/psychometric tools:

pedMIDAS – routinely collected

Dutch Eating Behaviour Questionnaire – Ages 12-16 – Child reported:

The Children's Dutch eating behaviour Questionnaire Ages 7 – 12 – Child Reported:

The Child eating behaviour questionnaire: (CEBQ) Ages 5 – 12 – Parent reported:

The Achenbach Child Behaviour Checklist (CBCL) – Ages 4 – 18 - Parent reported:

The Food Cravings Inventory (FCI) 5 - 16 yrs - Child reported

Food intake questionnaire (FIQ) 5 -16 yrs – Child reported

Body Mass Index (BMI) – Height and weight collected by the neurology clinic nurse routinely

2.2.1 Practicality of recruitment

The primary investigator identified potential participants for the study by two methods. Referrals to the neurology outpatient department from another health care professional (hospital consultant or general practitioner (GP) etc) all have a referral letter that is managed by the relevant consultant's secretary. Therefore, all secretaries were made aware of the study and were to highlight any new headache referrals to the primary investigator. For completeness, the primary reviewer also read through all neurology referrals once a week.

Furthermore, the primary investigator would read through the notes of all the patients who had an appointment with a paediatric neurologist (who managed headaches) prior to clinic on the days of headache clinics.

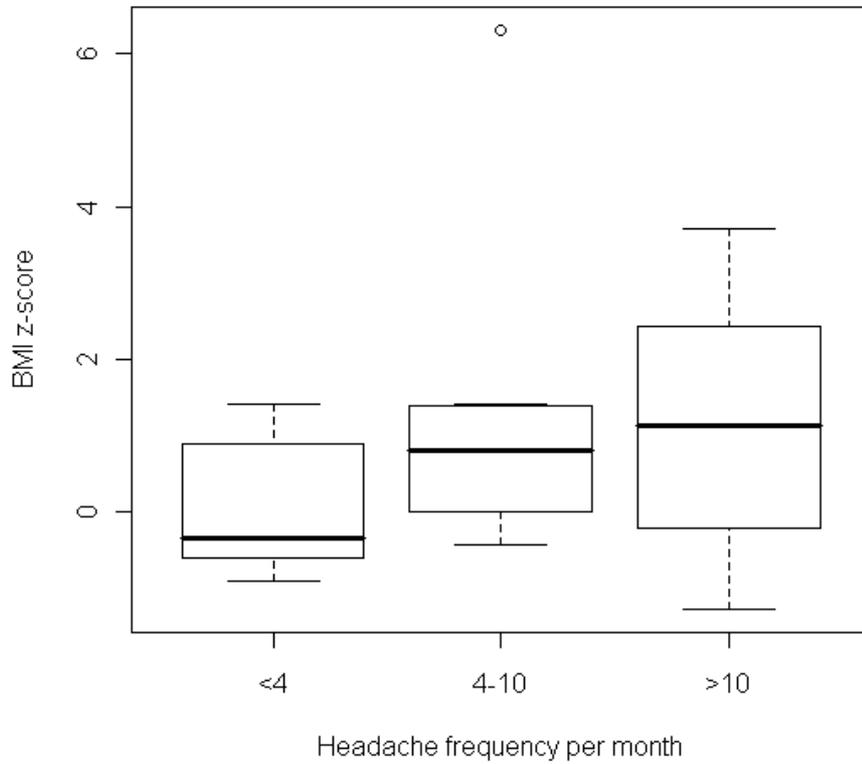
If a patient was identified to fit the criteria for study, the patient and their carer were approached regarding the study after their paediatric neurology clinic appointment At Alder Hey Children's NHS Foundation Trust Hospital. The study was discussed with the carer of the child, and an info sheet was given to the carer. The carer was then asked whether they would agree to be involved in the study, or whether they needed more time to think about the study. If they agreed to recruitment, they were then brought into a private room (allocated for the study), whereby consent and assent was taken from carer and participant respectively. The relevant psychometric tools were then applied to the participant and carer respectively, taking 30 minutes on average. The clinic nurse routinely collected participants weight and height; therefore the primary investigator also noted these. In the event that the carer was unsure whether to become involved in the study, the primary investigator simply asked whether they would mind being contacted about the study again? If they agreed, then their contact details were taken and a time to contact them was decided upon by the carer. If, upon further contact with the carer, they agreed to be recruited to the study, a date for them to attend the paediatric outpatient clinic was arranged. On this date the relevant psychometric tools were applied to the carer and participant in the same allocated private room. Recruited participants and carers were offered the opportunity to be sent the results of the study once it had come to completion. Note that the primary investigator recruited every patient in the study.

Chapter 2:3 Preliminary investigation to assess hypothesis (See Appendix E):

As a preliminary assessment of the designed hypothesis, relevant preliminary data of 45 patients was collected at the tertiary hospital neurological outpatients clinic. It was important to elucidate whether the study hypothesis had any scientific justification. Using routine clinical data the aim was to identify if the hypothesis could be supported by preliminary data before conducting a full pilot study. The data collected were from consecutive migraine referrals to the neurology department.

Details of patient's height, weight and headache frequency were collected. From this data, BMI z scores were calculated and headache frequency was categorised into: less than four headaches a month, four to ten headaches a month and greater than ten headaches a month. These were used as a predictor of headache severity. The results are shown overleaf.

Figure 6: Correlation of BMI z-score with headache frequency:



n=45

The results in figure 6 above show a trend of increased headache frequency being associated with increased BMI-z score. Note the outlier in the category 4-10 headaches per month, due to a morbidly obese participant. The results suggest that increased headache severity is weakly positively correlated with increased adiposity. Although the results were not statistically significant (most probably due to the small sample size of 45 patients) the trend fits into the hypothesis and supports the need for further focus on appetite behaviour.

CHAPTER 2:4 Research Methodology:

Chapter 2:4:1 The process of identifying the most suitable psychometric tools for the planned study and the details of each tool

2:4:2 Measure of migraine severity

To best assess the morbidity caused by migraine a tool was required which would measure both the frequency and severity of the headache, as predictors of morbidity. After a literature review a number of appropriate methods and psychometric tools were identified. The International Headache Society (IHS) scale(191) was one such tool; this was based on child activity whilst in attack. This tool was not appropriate for this study, the purpose of which was to focus on overall trait disability of migraine, i.e. the disability the headache causes the child overall, not just when in attack. Alternatively, the number of rescue medications the child used could be set as a severity predictor. This was not considered an appropriate method of assessing trait severity. Primarily, because participants were going to be new referral headache patients, many of whom would not have been prescribed rescue medication and secondly, because the consequences of the migraine headache, such as fatigue, can last much longer than the headache itself. The number of GP visits has been used as a predictor of severity(47), however, much of the morbidity of migraine, such as fatigue and poor concentration, would not be captured by this method.

Two further appropriate psychometric tools were identified, the paediatric migraine disability assessment score (pedMIDAS) and the headache impact test 6 score (HIT-6). The HIT-6 is a six-item questionnaire, which assesses the impact of the sufferer's headaches on their life. It assesses their ability to carry out usual activities, social functioning, their cognition and emotional distress(192). Scores range from 36 (lowest) to 78 (highest). A score of less than 49 equates to no or little impact, 50-55 reflects some impact, 56-59 reflects substantial impact, > 60 reflects severe headache impact(193). HIT-6 has been widely used as a tool to measure headache impact, but not for paediatric migraine.

The pedMIDAS is derived from the migraine disability assessment score (MIDAS), which is the most extensively used psychometric tool to measure the overall impact of headache on an adult patient in the previous 3 months. The pedMIDAS is also a 6-item questionnaire, which assesses headache disability during the previous 3 months. The tool records the impact headache has on school, home and social life. The number of days absence from school or social activity due to headache are recorded, as are the number of days on which headache causes participants to have at least 50% reduced ability in these settings or at home(11). PedMIDAS scores are the sum of the scores from the six questions, ranging from 0 to 270. A score of 0-10 indicates no disability, 11-30 a mild disability, 31 – 50 moderate disability and a score greater than 50 indicates severe disability(11).

Hershey et al have validated the pedMIDAS for its suitability in the paediatric population for which it was designed(11). The HIT-6 was costly and was designed for and validated in the adult population. In contrast, the pedMIDAS was a free tool to utilise and designed to be used in the paediatric population. Another potential questionnaire that was later discovered was the headache disability inventory. This questionnaire, however, is also targeted at adults and in the literature appears to have been superseded by the pedMIDAS. Another tool that could have been used to assess migraine disability was the paediatric Quality of Life measure. This tool, however, focuses only on the disability side of the migraine, not the severity and frequency of the migraine; a crucial part of the headache nature needed for our study. It was decided that the pedMIDAS was the optimum tool to measure the migraine severity in the planned study; it was designed for use in the paediatric population in contrast to the HIT-6. Furthermore it focused not just on the disability side of migraine, but the severity of migraine as well.

2:4:3 Measures of appetite behaviour

As previously mentioned, the primary outcome of the study was to correlate appetite behaviour to migraine severity, therefore, it was essential to utilise well validated, appropriate, psychometric tools to measure both. From the literature review it was clear that the Dutch Eating Behaviour Questionnaire (DEBQ) was a widely used tool for assessing appetite behaviours in the behavioural psychology domain. The authors of this tool were also the authors of a number of appetite behaviour concepts mentioned in chapter 1.3 and it was clear that this questionnaire was very relevant and would focus on the appetite behaviours in which we were interested.

Dutch Eating Behaviour Questionnaire – Ages 12-16 – Child reported

The Dutch Eating Behaviour Questionnaire (DEBQ) was developed by Van Strien et al in 1986(194). The questionnaire is completed by adolescents aged 12- 16 years old. It has been shown to be straightforward for adolescents to use(195). It consists of 33 items, which measure emotional eating (eating in response to certain emotions to cope with feelings or improve mood), external eating (eating because of external triggers and cues to eat, such as presence of food, rather than because of hunger or other internal cues) and restrained eating (defined by concern for dieting and weight fluctuation, leading to overeating episodes). There are 13 items to assess emotional eating, 10 items for external eating and 10 items for restrained eating. Every answer is rated on a scale 1 (never) to 5 (very often). The DEBQ scales have high internal consistency, high validity for food consumption, and high convergent and discriminative validity. Cronbach's alphas have been shown to be 0.92 for emotional eating, 0.84 for external eating, and 0.92 for restrained eating(133). The DEBQ has been widely used in adolescent studies of eating behaviour and obesity. External scores are most expected to change. This is based on literature that suggests there are greater external cues to food in obese subjects. There should also be more response to external cues in migraine due to the neurochemical mediators such as orexin causing an increased drive for food, however, emotional eating has been correlated with the CBCL internalizing score in previous work(196). Furthermore, it is known that internalizing scores are correlated with migraine and may, therefore, be confounding.

Although the DEBQ has been shown to be appropriate in adolescents (12-16) another simpler questionnaire was needed for younger children. After a further literature search the Dutch Eating Behaviour Questionnaire for Children (DEBQ-C) was discovered. This discovery was very timely, as the DEBQ-C was only validated in 2008(195), so the planned pilot study would be amongst the first to use this validated tool. It was crucial that the DEBQ-C was found, because it demonstrated that, in younger children, the normal response to stressors was loss of appetite, in contrast to the response of older children and adults who were prone to overeating.

The Children's Dutch eating behaviour Questionnaire Ages 7 – 12 – Child Reported

The Children's Dutch Eating Behaviour Questionnaire (DEBQ-C) was designed by the authors of the DEBQ (194). It is a child-reported questionnaire designed so that a reliable age adapted version of the DEBQ could measure restrained, emotional and external eating in 7 – 12 year old children. The DEBQ-C has been extensively analyzed in an initial pilot study and in two subsequent large-scale studies (769 participants and 515 participants respectively)(197). It has been reported that reliabilities of its subscales ranged from 0.72 to 0.82. Furthermore, good internal consistency was shown. Cronbach's co-efficients were 0.80, 0.72 and 0.68 for emotional, restrained, and external eating respectively(194). Being a 20-item questionnaire (rather than 33 items in the adolescent cohort) it would be more likely to be completed by participants with a short attention span. This questionnaire has only recently become commercially available and there are no reports of its use other than by the authors.

After a number of discussions with the appetite specialists it was decided a form of parent/carer reported psychometric tool for appetite behaviour should be sought, rather than solely rely on the accuracy of the participant's answers. Furthermore, in the case of children at the youngest end of the spectrum (as young as 5), it was felt that they might struggle to answer the questions accurately for a number of reasons e.g. not understanding the question or not being confident to answer a researcher. The Children's Eating Behaviour Questionnaire (CEBQ), found after a literature search, was

chosen as the parent reported psychometric tool, due to its robust structure and validation(198).

The Child eating behaviour questionnaire: (CEBQ) Ages 5 – 12 – Parent reported

The Child Eating Behaviour Questionnaire (CEBQ) is a parent reported questionnaire designed to assess eating styles related to obesity risk in young children (younger than envisaged for the DEBQ and DEBQ-C). It was designed to capture individual differences in aspects of eating style. It is a 35-item tool, with eight subscales. These are food responsiveness, enjoyment of food, emotional overeating, desire to drink, satiety responsiveness, slowness in eating, emotional under-eating, and fussiness. Cronbach's alphas have previously been shown to be 0.80, 0.91, 0.79,0.89,0.74,0.74,0.74 respectively(139). The CEBQ is accepted to be a very useful tool in measuring eating styles for research into the early precursors of obesity, thus it is entirely relevant for this study(198). It has been shown to have high internal validity and test-retest reliability. The ability to analyze parents' reports of the children's eating will be very useful for the proposed study. The study includes the combined Satiety-responsiveness and enjoyment of food scales as used by Wardle et al in their study of the FTO gene(110). The study design also includes the self-report DEBQ-C and the parent report CEBQ in the children aged 7-12 years since it is not clear in the literature how these two scales overlap.

Another area this study was interested in addressing, as a secondary outcome, was the cravings aspect of patients' appetite behaviours. As mentioned in the literature search, Blau et al informally studied cravings around the time of migraine(151). No trait cravings have, however, hitherto been studied in the paediatric population. If patients have aberrant appetite behaviours e.g. overeating, it is plausible that they will have cravings for particular foodstuffs. To give an example, it has been shown that schizophrenic patients have aberrant appetite behaviours and, furthermore, have a predilection for excessive consumption of high fat, processed foodstuffs(199). It is important, therefore, to highlight if migraine, another chronic disease, causes cravings for certain types of food. Following extensive discussion with behavioural psychologists in the area of appetite, it

was decided that the food cravings inventory was the most appropriate tool for the aims.

The Food Cravings Inventory (FCI)

The food cravings inventory (FCI) is another psychometric tool to be utilised as an indicator of the types of food that migraine patients crave (on migraine free days) and the degree to which they crave them. The FCI is a validated 28-item self-report measure of general and specific food cravings(126).

Cravings are defined as “an irresistible urge to consume a specific food(200)”. Participants rate the frequency of cravings over the past 30 days on a 5-point LIKERT scale ranging from 1 (not at all) to 5 (nearly every day). The FCI is composed of four conceptual factors (scales): (1) cravings for high fat foods (e.g. fried fish); (2) cravings for sweets (e.g. cake, chocolate); (3) cravings for carbohydrates/ starches (e.g. bread, baked potato) and (4) cravings for fast food (e.g. pizza, burgers). From this a total score is also calculated. Subscale scores can be calculated for individual items, with higher scores indicating more frequent cravings for a particular food category. The scales have been characterized by exploratory factor analysis and confirmed with confirmatory factor analysis. The reliability and validity of the FCI has been established(201). Furthermore, the high fat food scale has been found to distinguish obese from lean individuals. In a previous obesity study Cronbach’s alpha coefficients showed cravings for: - 1) fats - 0.81, 2) sweets - 0.83, 3) carbohydrates - 0.76, 4) fast foods - 0.70 (202). The inclusion of this tool in the study will help map particular cravings in trait migraine that may help elucidate areas that lead to aberrant appetite behaviours.

Following discussions with behavioural psychologists in the field of appetite, it was decided it would be important to highlight what typical foods the child eats in a day. Two relevant psychometric tools were available; the food frequency questionnaire and the food intake questionnaire. The former enables estimates of nutrient intake whilst the latter records what foods the patient has eaten on the previous day. Whilst the food frequency questionnaire would give more data with regarding specific nutrition, this was not necessary for our study. Capturing the typical foods being eaten by migraine patients was the aim, therefore after discussion with one of the

authors of food intake questionnaire(203), it was decided the FIQ would be incorporated into the study.

Food intake questionnaire

The Food Intake Questionnaire (FIQ)(203, 204) is a self-administered patient questionnaire, which requires a 24-hour recall method. The questions relate to consumption of particular foods on the previous day. The basic stem question is “Did you at any time yesterday eat any amount of.....(204)” followed by a list of food related items. The questionnaire has been used extensively in Liverpool(205, 206), in large populations of school children to produce large volumes of normative data.

The FIQ has been shown to be highly validated and have good reliability. Reliability of the FIQ was assessed by comparing mean scores for each food group using Pearson correlation coefficients. All correlations ranged from 0.41 to 0.76. Previous studies have shown that the FIQ should detect a change of +/- 10% in eating behaviour(203). There are two large scale studies, each carried out on more than 700 school children in Liverpool(205, 206), which produced normative data on patterns of what children eat.

Psychometric tools used as outcome measure for secondary outcomes:

Chapter 2.4.4 The Achenbach Child Behaviour Checklist (CBCL) – Ages 4 – 18 - Parent reported

The child behaviour checklist (CBCL) is a commonly used parent-reported psychometric measure that assesses emotional and behavioural problems in children aged 4-18 years. The first part concerns social skills, participation in organizations, contact with friends, participation and skills in sports and academic performance ratings. The second part deals with emotional and behavioural problems classified as internalized or externalized. Internalized behaviour problems are those that essentially the child himself experiences; they include anxiety/depression, withdrawal, schizoid, and somatic behavioural problems. Externalized problems are overt in nature, with direct effects on others: they include delinquency as well as cruel and aggressive behaviour. The CBCL consists of 113 items, which are scored on a 3-point Likert scale to indicate how descriptive the items are of the child during the

preceding 6 months. There are two broadband scores representing internalizing and externalizing problems and 8 narrow band behaviour scales are used within this. The CBCL exhibits good reliability and validity. When previously used in a migraine cohort of 47 patients, maternally reported scores for internalizing behaviour were 57.18 (S.D 10.15) in migraineurs compared to 49.84 (S.D 8.83) in controls with a Cohen's effect size of 0.80; externalizing behaviour was 53.66 (S.D 10.09) in migraineurs vs. 49.87(S.D 12.74) in controls with a Cohen's effect size of 0.24(197). When previously used in an obesity cohort of 155 children, obese patients had an internalization score of 58.9 (10.9S.D) compared to controls 53.4 (10.4 S.D) and externalization score of 52.6 (SD 10.6) compared to controls 48.1 (9.5 S.D). This gave an effect size of 0.010 and 0.004 respectively. (207). For clinical use the scores of the CBCL are calculated into T-score cut offs to assess whether a patient is exhibiting a particular psychological trait. Alternatively, mean and standard deviation scores can be used and compared with normal population scores.

Previously, test – retest reliability correlations were between 0.82 and 0.95 for the eight subscales and 0.93 for the total problem score(208). This is a well-recognised tool used in routine clinical care at Alder Hey, and used in numerous studies of childhood migraine and eating behaviour, henceforth it is a logical tool to incorporate in our study to understand whether psychological factors are a confounder in the planned study.

The final task was the design of an informal migraine pro forma, which was an adapted pro forma published in the book “headache in Childhood and adolescence(209)”, to capture and classify what type of migraine the patient had.

As demonstrated above, great thought, discussion and time were spent trying to determine the optimum tools to address the hypothesis. In essence, the project lies not strictly within medical research, nor fully within psychological research and in consequence, the synthesis of both areas with appropriate tools was a laborious one. Once the appropriate tools were designed, a large number of drafts of protocol were designed. In total fifteen iterations of the protocol were drafted and, once completed, were submitted

to the local ethics committee and research and development department. The length of time for favourable opinion was considerably longer than anticipated, and is discussed in the limitations section (section 6.4) of this thesis. It is important to highlight that whilst the protocol design and ethics applications were taking place two studies were published assessing obesity associated with migraine severity in the paediatric population(106, 107). These publications highlight the timeliness of the planned study, as internationally this area is gaining focus and interest. Furthermore, it highlights the originality of the study design. Unlike the aforementioned studies, both focusing on correlating weight with migraine disability, the focus on appetite behaviour in the study was novel.

Chapter 2.4.5 Summary of psychometric tools to be utilised in study

All psychometric tools below were answered at a one off interview with the participants:

PEDMIDAS – *Measures headache severity*

Dutch Eating Behaviour Questionnaire – Ages 12-16 – Child reported – *Measures appetite behaviours*

The Children’s Dutch eating behaviour Questionnaire Ages 7 – 12 – Child Reported - *Measures appetite behaviours*

The Child eating behaviour questionnaire: (CEBQ) Ages 5 – 12 – Parent reported - *Measures appetite behaviour*

The Achenbach Child Behaviour Checklist (CBCL) – Ages 4 – 18 - Parent reported - *Measures behavioural psychology*

The Food Cravings Inventory (FCI) 5- 16 yrs – Child reported – Measures food cravings

Food intake questionnaire (FIQ) 5 -1 6 yrs – Child reported - *Measures food intake*

Body Mass Index (BMI) – *Measures weight.*

Chapter 2:5 Methods of Data analysis

Below are the statistical analyses employed for the study:

Univariate analyses with appetite behaviour as dependent variable:

- Pearson's correlation between PedMIDAS score (measure of migraine severity) and CEBQ and DEBQ eating behaviour subscale scores.
- ANOVA will be utilised, using categories of migraine severity, dependent variables are CEBQ score and DEBQ score as above.

Multivariate analyses with eating behaviour as dependent variable:

- PedMIDAS, CBCL, BMI, sex, age, as independent variables, with eating behaviour scores as dependent.
- Univariate analysis for the migraine effect with adiposity as the dependent variable, as reported in previous studies (chapter 3.2).
- Pearson's correlation between PedMIDAS score (measure of migraine severity) and BMI z-score (measure of adiposity).

Multivariate analysis- a mediation analysis to demonstrate migraine acts through eating behaviour to cause effect on adiposity

- Multivariate analysis using eating behaviours scores and PedMIDAS migraine severity scores as independent variables and BMI z-score as dependent variable.
- A descriptive analysis of food cravings and other dietary behaviours.
- Sample size discussed in chapter 2.2.

CHAPTER 3: literature review results:

Chapter 3.1 Critical analysis of each relevant study:

To formally critically analyse the previous studies in the relevant area of research, the Strengthening of The Reporting of Observational studies in Epidemiology (STROBE)(170) tools (refer to Appendix C and D) were utilised. Individual tools for each type of study e.g. case control were available to apply to the relevant studies. STROBE is being endorsed by a growing number of biomedical journals to improve the rigour of published work. It was not necessary, in this case, to design more formal inclusion criteria, for a systematic review of the literature in order to certify high quality studies, because there were so few studies in this area of interest. If a larger volume of studies existed in the area, formal inclusion criteria would have been adopted. All of the relevant studies in this area have been included below.

Chapter 3.1.1 Study 1: Obesity and migraine: A population study. Bigal ME et al(44)

This study was a population based, cross-sectional study. The methodology was a population based telephone interview. There were 30,215 participants recruited into the study over a three year time period. The aim of the study was to assess the influence of BMI on headache prevalence, frequency, severity, disability and associated headache symptoms. The study predicted, based on previous work showing that the odds of chronic daily headache were five times greater in obese patients (104), that obesity would be associated with migraine prevalence and severity. The study gave a reasonable biological plausibility, citing the overlap of CGRP and inflammatory markers in both pathologies.

The methodology of the study was contacting a large population sample using a computer-assisted telephone. Participants were firstly screened for eligibility. Eligible consenting participants then agreed to a scheduled telephone interview. Large amounts of data were recorded regarding participants' headaches. This included frequency and severity (using a scale

of 1 -10) of headache and covered all necessary questions for diagnostic criteria of migraine in the IHS. Participants were also to self report their height and weight so that their BMI could be calculated. Baseline demographic data was also assessed. A thorough discussion of the statistical methods was given.

Results of the study showed that migraine prevalence did not statistically significantly differ in overweight, obese, or morbidly obese categories when compared to normal weight patients. This is contrary to this study's hypothesis. In keeping with the hypothesis, however, high BMI was associated with increased headache frequency. In comparison to 4.4% of normal weight participants having 10-14 headache days per month, 5.8% of overweight (OR 1.3), 13.6% of obese (OR 2.9) and 20.7% of morbidly obese (OR 5.7) had 10-14 headache days per month. Furthermore, BMI was also a predictor of migraine features. Participants with sequentially higher BMI reported sequentially greater number of headache features, a predictor of severity.

The crucial findings of this paper highlight that increased BMI was not associated with increased migraine prevalence. In keeping with the previous longitudinal migraine obesity study by Scher et al(104), however, obesity was associated with increased headache frequency. Further findings were that BMI was associated with severity of migraine, and a number of migraine features, such as photophobia. Because the study was cross sectional, the authors did not imply any causality in the migraine obesity relationship.

A number of limitations to this study were highlighted when critically appraised using the STROBE tool for cross sectional studies. Firstly, no potential confounders were discussed in the methodology of the study. Furthermore, there was no discussion of how sample size was arrived at. Sources of bias were not identified in the methodology, nor were missing data identified in the study. Similarly, numbers of participants at each stage of recruitment were not highlighted.

The authors did highlight some other limitations. Firstly, they attributed the over representation of females (65%) in the study to phone calls taking place

in business hours. Secondly, they highlighted that food triggers were not addressed in the survey. The authors suggested that they expected less food avoidance in increased BMI groups, but this was not assessed. Equally, depression, a co-morbidity of both diseases, was not formally addressed. Most importantly, they highlighted that the largest limitation of the study was that height and weight were self-reported by participants. They suggest that obese participants may have under-reported their weight, and this may have reduced the effect size of the study's findings.

The findings of this study are important; it is the largest study in this area of interest. It strongly augments previous work, underlining the link between obesity and the frequency and severity of migraine. Furthermore, it does not negate the theory of this thesis; this being a cross sectional study, causality can only be postulated, as in all previous studies. It remains plausible, in keeping with the hypothesis of this thesis, that migraine could cause poor appetite leading to obesity, and this obesity then worsening migraine.

Some of the limitations of this study offer insight into how to structure the pilot study design. For example, it will be important to address avoidance of food triggers in the cohort of patients. It will be interesting to see if there is a consistent trend between patients of different weight. Furthermore, it will be interesting to see if there is variation of food avoidance in patients with varying appetite behaviour. It is plausible that those with most aberrant appetite behaviour scores would avoid food triggers the least. Similarly, this study suggests those with highest BMI avoid food triggers least.

Chapter 3.1.2 Study 2: Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Bigal et al(100)

This study was a population based cross sectional study. The methodology was, again, a telephone based interview. It was a very large population of 30,215 participants, recruited over a three-year period. The aim was to assess the influence of BMI on chronic daily headache and, in particular, its two most common subtypes, chronic migraine and chronic tension type headache.

The results showed that BMI had a strong influence on chronic migraine (OR 2.2 in the obese category), but that BMI influence on chronic tension type headache was not significant. It appears from scrutinising this paper that this study is a sub section of study one above. The recruitment was at the same time period and the number of participants is identical. At no point during the published paper do the authors explicitly highlight if this is the case. This ambiguity is a limitation of the study. Given that the explanation of the methodology is identical in this study as for study one, it is reasonable to conclude that both studies are from the same recruitment process. It appears that the authors have conducted a sub analysis of the participants with chronic daily headache (1,243 participants) from their original large population. From this sub group they have correlated the different types of chronic daily headache against BMI, to yield the results mentioned above. As such, the limitations from study one (above) also applicable to this study.

Chapter 3.1.3 Study 3: Factors associated with the onset and remission of chronic daily headache in a population-based study. Scher et al(104)

This study was a population based longitudinal case control study. There were 1932 participants (1134 cases and 798 controls). The aim of the study was to describe factors that predict chronic daily headache ((CDH - defined as 15 or greater headaches a month) onset or remission in an adult population. The methodology of the study was that patients were put into the case category if they were recorded to have 180 headaches or more per year and control category if they had between 2 and 102 headaches per year. 55,255 patients were recruited at baseline into the study. Patients with 103-179 patients were not included in the study. The authors used a broad headache frequency for the control arm, to assess whether baseline headache frequency was a risk factor for CDH onset. There were 798 controls and 1134 cases available for follow up phone interview at 11 months. Large amounts of data were recorded pertaining to the marital status and physical attributes of patients at baseline. Of interest to the planned study, the BMI of all participants was based on participant self report of height and weight at baseline and follow up.

The results of the study showed two important findings. Firstly, the prevalence of chronic daily headache was associated with obesity (BMI > 30). Secondly, the development of CDH was associated with obesity. In other words, at baseline interview the population cases of CDH were found to have a significant association with obesity. At follow up interview, the incident cases of CDH (i.e. increase in headache frequency from 2-104 to >180 in the time frame of 11 months) was significantly associated with obesity.

This study is important for a number of reasons. Firstly, it is the only longitudinal data focused on the association between migraine and obesity. Secondly, it is an adult based study thus, although one can postulate cause and effect of migraine and obesity, causality remains unclear. Essentially, causality cannot be determined in participants with established migraine and established obesity. It remains plausible that migraine could have caused poor appetite behaviour leading to obesity, which subsequently caused migraine transformation, rather than the reverse. The fact that it is in an adult population obfuscates the cause and effect of this relationship, again highlighting the need for the planned study in a paediatric population.

Chapter 3.1.4 Study 4: Headaches in Overweight Children and Adolescents Referred to a Tertiary-care Centre in Israel. Pinhas-Hamiel et al(106)

This study was a questionnaire based case control study in a paediatric population in Israel. The aim was to “assess the association between obesity and primary headaches in children and adolescents(106)”. The crucial finding of this paper was that obese adolescent female participants had a four times greater risk of headache than participants of normal weight. The discussion of links between the two diseases is limited. The focus is on co- morbid conditions such as hypertension, along with discussion on excessive television watching being linked to both conditions. There was no mention of neurobiological plausibility throughout the study. Importantly, the study is very vague in explaining its methodology and recruitment process and at no point explicitly defines the study as case control. Only from scrutinizing the paper at length does this become clear. Obese cases were recruited from a tertiary endocrine clinic and controls from a general paediatric clinic. Once

this is established it becomes clear that they present their results in a very unorthodox fashion. To clearly exemplify this a table (table 3) is needed:

Table 3: Cases and controls in Pinhas-Hamiel et al(106) study:

	Headache	Not Headache
Overweight/Obese (case)	27	130
Normal weight (Control)	12	104

The exposure in this study is migraine; overweight and normal weight patients (underweight patients were not recruited) were recruited from an endocrine and general paediatrics clinic respectively, to assess whether or not they have headache. Once the cohort of 39 patients migraine patients were found, however, they were re-examined to address the patient's weight. Thus the results are presented as if weight (i.e. obesity) is the exposure for headache, when in fact the reverse is the case. This could possibly be why the design of the study (case control) is obfuscated somewhat. Furthermore, their pre-specified hypothesis is equally vague. There is no direct discussion of primary and secondary outcomes.

A strong feature of the study is that it gives a description of the variables that would be considered in analysis. It gives an in depth discussion of the statistical methods employed and discusses the logic behind the power calculation sample size of 120 children in each group. This calculation yielded an 80% power to detect a two-fold difference between children of normal weight and overweight children. The authors even explicitly highlight the caveat that the power calculation is based on the assumption that the prevalence of headaches in children is 15%. They also highlight that the interpretation of results should be taken with suitable caution, highlighting limiting factors such as the study being underpowered, and several co-variables, such as exercise patterns not being assessed.

There were, however, weaknesses in the results component of the study: numbers of individuals at each stage were not reported e.g. potentially eligible, reasons for non-participation were not cited and characteristics of participants were not comprehensively state.

This study highlights a number of interesting issues. The key finding is that it female, but not male, overweight participants were at increased risk of headaches. The authors offer no explanation of why there is discrepancy between the sexes. It is the only case control study focusing on headache and obesity in children. It has only been published in the time that this MPhil has been conducted, highlighting the timeliness of the proposed study. The study itself highlights that females have a four times greater risk of headache. Although this result is persuasive, it must be regarded with caution, considering the unconventional presentation of methodology and results discussed above.

The study also includes all types of primary headache, including tension type headache. As mentioned in the neuropeptides section (section 1.4), migraine and specifically migraine with aura, is arguably the most biological headache; that being that there is a very complex pathophysiology underlying the disease. In contrast, for example, to medication overuse headache, which has a clear straightforward reversible stimulus. Migraine is also considered to give the greatest morbidity to its sufferers. Thus, in fitting with this thesis, it is unsurprising that the association of any primary headache with obesity is relatively small (in males there was no difference in headache prevalence between the weight groups). Hence the planned study will focus on migraine severity and appetite behaviour (as a predictor of adiposity) aiming to offer an insight as to whether a severe, complex biological headache, i.e. migraine will have stronger association with poor appetite behaviour and subsequent obesity than general primary headaches was found to in Pinhas-Hamiel's study. Pinhas Hamiel's study pontificated cause and effect between paediatric headache and obesity. As aforementioned, however, no causality can be determined in a study where both migraine and obesity are already established. Thus, the planned study is no less valid; rather it highlights the need for cause and effect to be established.

3.1.5 Study 5: Obesity in the paediatric headache population: A multi centre study. Hershey et al (see Appendix E)(107)

This study was a retrospective case series analysis of 913 consecutive migraine patients in seven specialist headache paediatric centres. The objective of the study was three-fold: Firstly, to assess the prevalence of obesity in migraine patients; Secondly, to examine the relationship between obesity and frequency and disability of headache and, thirdly, to examine the effect of weight change on headache frequency and disability. The authors hypothesised that prevalence and frequency of migraine would be increased in obese patients, based on the previous findings by Bigal et al(44).

The methodology of the study is obfuscated somewhat in the publication. It initially appears as if patients were recruited prospectively and administered the pedMIDAS tool (as a measure of their headache disability), with their height and weight being measured simultaneously. By further scrutiny it becomes clear that this is a very simple study design. It is, in essence, a retrospective case-only analysis of patients who have been routinely administered pedMIDAS at clinics and had their height and weight measured.

The results showed that obesity levels were high, with 34.1% of participants categorized as either at risk of overweight (85-94th BMI percentile) or overweight (95th BMI percentile or above), but this did not statistically deviate from estimated U.S prevalence (107) of obesity in the paediatric population. The study did show that BMI percentile was significantly correlated with headache frequency and disability (measured by the pedMIDAS); however, the association of BMI percentile with headache frequency ($r=0.10$, $P=0.03$) and disability ($r=0.10$, $P=0.2$) were only modest. One reason for this could be the incorporation of all primary headache types into the study. Previous associations between headache and obesity have been specifically between migraine and obesity(109); it has been shown that chronic daily headache and obesity are linked(100), and that increased BMI increased migraine frequency(44). The authors accepted that one cannot derive causality in the relationship between the two pathologies due to the nature of this study. The authors did cite the commonly known

neurobiological overlap to highlight the association. The authors highlight the need for further study in this area to establish the underlying mechanism that relates the two diseases. This study again underlines the need for the proposed study, to see if appetite behaviour has a role in the intermediary step between migraine and obesity. Hershey et al have certainly highlighted that the obesity and migraine relationship exists in the paediatric population as well as the adult population; however, they shed no light on the causality of the relationship between the two. Obese patients that have headache may have previously been normal weight and still had headaches prior to the onset of their obesity; this cannot be elucidated from their study due to the methods employed in the work.

3.1.6 Study 6: Obesity and paediatric migraine. Kinik et al (108)

This study was a retrospective case series of 124 migraine patients in a paediatric neurology clinic in Turkey. It aimed to assess the influence of BMI on migraine severity and frequency. Secondly it assessed the influence of BMI on associated migraine symptoms.

The methodology of this study was straightforward; 124 patients' notes were accessed over a six year period and the following data were collected: characteristics of headache frequency over the last three months, severity based on a verbal report of a 1-10 scale and associated symptoms such as photophobia and phonophobia. Their method of weight measures was original, utilizing relative BMI ((relBMI) = $\text{BMI} \times 100 / 50^{\text{th}} \text{ percentile BMI}$ for patient's age and sex). This calculation is the individual's BMI divided by a standard BMI for their sex and age(210). The advantages of this are that it can help standardise BMI across age and sex and it allows you to follow tracking and changes in BMI as more accurately(210). Using this method, normal weight was a score of <110, overweight 110 -120, obese >120.

The study showed a number of interesting findings. Obesity prevalence of this cohort of migraineurs was 17.7%; significantly higher than the latest obesity figures for this age grouping in Turkey (6.1%)(211). In keeping with the large adult population study by Bigal et al(44), there was a statistically significant correlation between obesity and increased migraine frequency (headache frequency per month - obese 5.3%, overweight 4.4%, normal

weight 3.8% - $P=0.018$). In contrast to Bigal et al(44), however, they did not find a significant association between relBMI and migraine severity or relBMI and associated symptoms.

The discussion of the findings in this study is poor. Firstly, the authors offer no consideration of how to reduce bias, nor do they offer any limitations of their study. They do not highlight any missing data; furthermore, they give no indication of the recruitment process, for example, whether patients were consecutively recruited, which leaves the reader to assume this was not the case. There is no interpretative explanation for the disparity between their study and the Bigal et al(44) study, which showed a statistically significant association between increased weight with increase in severity and associated symptoms. The majority of the discussion merely highlights the findings of other studies rather than focusing on their own.

The strength of the study is that this is the first paediatric population where specifically migraine (as opposed to all primary headaches) severity and frequency have been correlated with predictors of weight. Thus it is an important finding that, as in the adult population, obesity was associated with increased migraine frequency.

Another strength of the study is that it highlights the importance of orexin A and B in the overlapping neurobiology of migraine and obesity. The majority of other studies overlook these important neuropeptides.

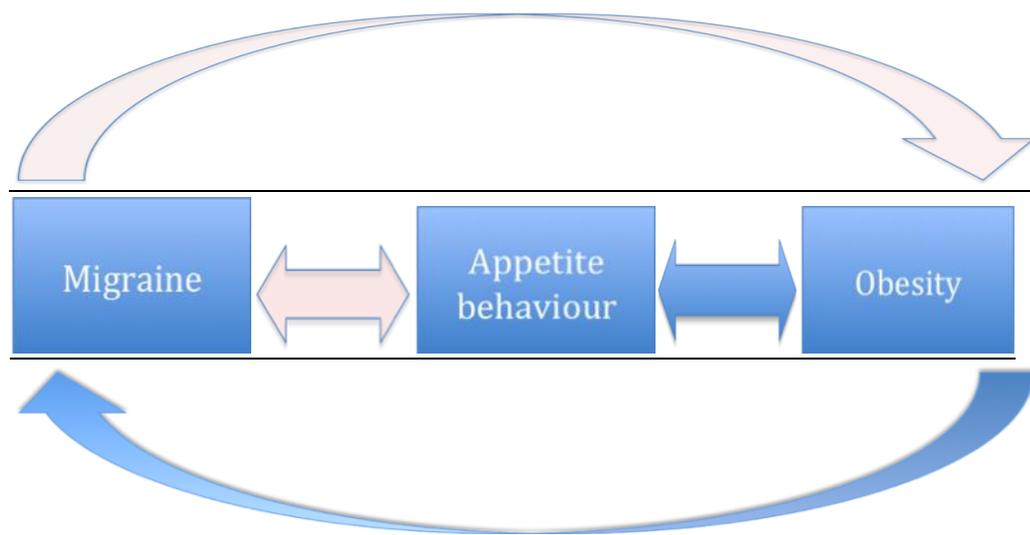
Overall, this study has a basic methodology and the key finding is that once more obesity was associated with migraine frequency, but this time this has been found in the paediatric population. It did not show an association with migraine severity and obesity. Once again causality cannot be derived from these findings, this being a cross-sectional retrospective case series, however, it is clear that this study has a very similar hypothesis to the large population study by Bigal et al(44), and is looking at the relationship from the perspective of obesity worsening migraine.

Table 4: Summary of studies addressing the relationship between migraine and obesity hitherto

Authors	Sample size	Study design	Method	Results
Scher et al	1932	Prospective longitudinal case-control design.	Two phone interviews at 0 and 12 Months – address factors that influence onset or remission of CDH.	Odds of CDH were five times Higher in obese and 3x higher in overweight Compared to normal weight.
Bigal et al	30,215	Cross sectional, population based telephone survey.	Population-based, telephone interview – to assess influence of BMI on headache severity and frequency.	Odds of having very frequent headache 2.9 in obese and 5.7 in severely obese compared to normal weight.
Bigal et al	30,215	Cross sectional population based telephone survey.	Population-based, cross-sectional survey - assessing the relationship between obesity and several episodic headaches.	Obesity was strongly associated with increased frequency of headache.
Pinhas-Hamiel et al	178	Case – control questionnaire based study.	Questionnaire and anthropometric measurements – to assess prevalence of headache in obese and overweight.	Female headache patients had a four times greater risk of obesity.
Hershey et al	913	Retrospective case –series.	pedMIDAS and anthropometric measurements - to assess effect of obesity on migraine prevalence, frequency and severity.	Obesity associated with headache frequency, but not prevalence.
Kinik et al	124	Retrospective case-series.	Migraine severity scale (1-10), Headache frequency and relative BMI (relBMI) was collected to assess relationship of weight on headache severity and frequency.	Obesity associated with increased migraine prevalence and frequency, but not severity.

Table 4 is a summary of all the studies highlighted in the formal literature search studies that focused on the migraine and obesity relationship. The first three are adult studies whilst the latter three are paediatric studies.

Figure 7: Reviewing the direction of causality in migraine, appetite behaviour and obesity



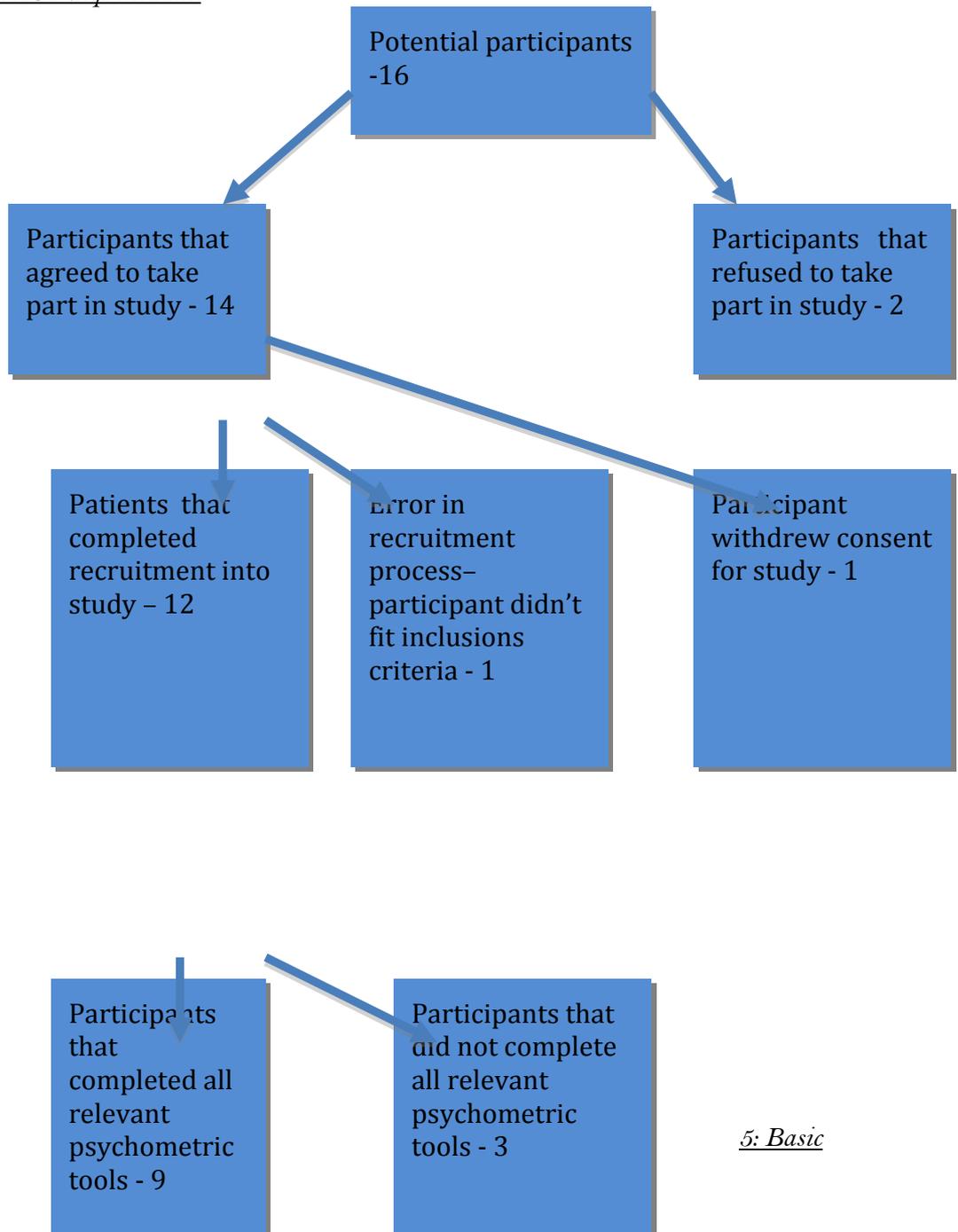
From the hypothesis generation and critical analysis sections of this thesis, it is clear that in work hitherto that there is a relationship between migraine and obesity. From the formal literature review, it is clear that hitherto no work has established the cause and effect of the relationship between migraine and obesity. This is highlighted in this diagram (figure 7) by the large blue and pink arrows. The direction of effect remains elusive. Furthermore, the appetite behaviour section should highlight comprehensively the evolving link between appetite behaviour and obesity. The blue two-way arrow represents this. This pilot study's hypothesis is that due to the underlying neurobiology, migraine causes aberrant appetite behaviours, which may lead to increased adiposity and subsequent onset of obesity. This is indicated by the large pink arrow, and is yet to be formally studied. To firmly test such an association, a large longitudinal study is necessary. Thus, this pilot study aims to correlate whether increased migraine severity is associated with increasingly aberrant appetite behaviours (represented by the two way pink arrow). This will be a crucial stepping-stone to the overall hypothesis.

Chapter 4: Results:

4:1 Primary outcome results:

Figure 8 below highlights the response rate in the preliminary recruitment of the study. Only 56% of potential participants fully completed the psychometric tools.

Figure 8: Response rate



Table

5: Basic

demographics of participant population:

Category	Classification	N	%
Sex	M	3	30
	F	7	70
Race	White British	10	100
	Other	0	0
Age	5-12	4	40
	13-16	6	60
BMI	Underweight	0	0
	Normal weight*	9	90
	Overweight*	1	10
	Obese*	0	0
Diagnosis	Migraine	10	100
	Not migraine (control)	0	0

* N.B based on BMI z-scores.

Table 5 is a simple summary of the demographics of the participant population. It is clear to see the very small sample size recruited. All participants were white British and the vast majority were normal weight. There were more females recruited into the study. All participants were migraine sufferers.

Table 6: Dutch eating behaviour questionnaire scores:

Population	N=9	Emotional eating M(S.D)	External eating M(S.D)	Restraint eating M(S.D)
Both sexes	N=9	1.62 (0.57)	2.23(0.61)	1.58(0.75)
F	N=7	1.66 (0.62)	2.32(0.41)	1.66(0.83)
M	N=2	1.48(0.46)	1.99(1.26)	1.3(0.42)
Age 9-12	N=3	1.23(0.28)	1.93(0.85)	1.13(0.23)
Age 13-16	N=6	1.82(0.59)	2.4(0.41)	1.75(0.78)

4:1:2 Description of Dutch Eating Behaviour Questionnaire findings

Table 6 shows the mean scores of the three categories of appetite behaviour addressed by the DEBQ in the cohort studied. The average male migraineurs' emotional eating score was 1.48, which is within the average range (1.24-2.84)(132). The average female migraineur score of 1.66 is within the average range (1.31-1.68)(132). The average range is defined by the DEBQ user manual, which categorises the three separate strands of appetite behaviour into below average, average and above average aberrant behaviours based on large population norms. The average male migraineurs' external eating score was 1.99, which is in the 'below average' category (<2.18)(132). Similarly, female migraineurs' score of 2.32 was in the 'below average' category (1.89-2.49). The average male migraineurs' restraint eating score of 1.3, within the average category (0.92-2.12)(132), whilst the average female migraineurs' score of 1.66, was in the 'below average' category (1.30-1.84)(132). There were no data in the Dutch eating behaviour manual to formally compare age ranges with comparable age categories, It can be noted, however, that between age groups in this migraine population, external, emotional and restraint eating scores were consistently higher in the elder age range.

Due to the unexpectedly small sample size yielded in the study, it is futile to conduct statistical correlations between the DEBQ and pedMIDAS, nor the CEBQ and pedMIDAS, because it would be erroneous and unscientific to draw any meaningful conclusions from such a small sample size.

Table 7: Childrens Eating Behaviour Questionnaire scores:

	Overall	M	F	Age 5-12	Age 12-16
N	10	3	7	4	6
Satiety Responsiveness	2.9(0.77)	3.1(1.47)	2.83(0.37)	3.35(0.75)	2.6(0.69)
Slowness in Eating	2(0.73)	2.33(0.80)	2.1(0.87)	2.25(1.06)	1.84(0.44)
Food Fussiness	3.61(0.94)	3.6(1.51)	3.62(0.76)	3.67(1.30)	3.57(0.76)
Food Responsiveness	2.18(1)	1.73(0.64)	2.37(1.1)	1.75(0.57)	2.47(1.2)
Enjoyment of Food	3.36(0.88)	3.1(1.76)	3.5(1.02)	2.94(1.18)	3.5(1.1)
Desire to Drink	2.57(1.22)	2.33(1.53)	2.67(1.18)	1.58(0.69)	3.23(1.04)
Emotional Undereating	1.88(1.04)	1.5(0.866)	2.04(1.12)	1.75(0.87)	1.89(1.32)
Emotional Overeating	1.55(0.51)	1.25(0.25)	1.68(0.55)	1.63(0.63)	1.5(0.47)

4:1:3 Description of CEBQ scores

Table 7 shows the mean scores of the eight categories of appetite behaviour addressed by the CEBQ in the cohort studied. Migraineur scores from this study were compared to normal population CEBQ score averages from the author's of the CEBQ original validation of tool study(198). Overall migraineurs have a lower than average satiety responsiveness of 2.9 (mean 3.1)(139). Females have a lower satiety responsiveness than average 2.83 (mean 3.1)(139) whilst males have an exactly average score 3.1 (mean 3.1). The average scores are the normal scores recorded by the authors of the tool when validating the tool(139).

Both males and females independently had a lower slowness in eating score

than average, with 2.33 (average 3.1) and 2.1 (average 3.2) respectively(139). Elder migraineurs showed more pronounced fast eating rates (1.84) compared to younger migraineurs (2.25)(139).

The overall migraineurs' score for slowness in eating was below average 2 (average 3.15)(139) (139). Food fussiness was above average in the population, being 3.61 (average 3)(139). Both migraine girls and boys independently had a higher satiety score, being 3.62 (average 2.9) and 3.6 (average 3.1) respectively(139).

Food responsiveness of the overall population was just below average, being 2.18 (average 2.25)(139), however, there was a difference between the sexes. Female migraineur scores were just above average 2.37 (average 2.3). Males migraineur scores of being 1.73 were below average (average 2.2)(139).

Enjoyment of food scores for the whole population were below average at 3.36 (average 3.6)(139). Independently, male migraineurs' scores were substantially below average at 3.1 (average 3.6)(139), whilst female migraineur scores were just below average at 3.5 (average 3.6)(139).

Desire to drink scores for the population were below average at 2.57 (average 2.9) (139). Females migraine scores were independently below average, being 2.67 (average 2.9), as were male migraine scores, being 2.33 (average 2.3)(139).

The overall scores in this population for emotional under eating were lower than average, being 1.8 (average 3.05)(139). Male migraineurs scored substantially under average, scoring 1.5(average 3.1). Similarly, female migraineurs scored under average scoring 2.0 (average 3.0)(139).

The overall score for the population for overeating was 1.5, which is less than the average mean (1.8). Both male migraineurs, scoring 1.2 (average 1.8), and females migraineurs, scoring 1.6 (average 1.8), achieved under average scores.

Table 8: Paediatric Migraine Disability Assessment Questionnaire scores:

<u>Patient</u>	<u>pedMIDAS score</u>	<u>Severity</u>	<u>Frequency</u>	<u>Severity</u>
<u>1</u>	3	0	8	4
<u>2</u>	0	0	4	5
<u>3</u>	11	1	2	8
<u>4</u>	21	1	12	10
<u>5</u>	120	3	30	9
<u>6</u>	34	2	8	6
<u>7</u>	5	0	2	10
<u>8</u>	12	1	3	9
<u>9</u>	0	0	3	4
<u>10</u>	43	2	30	9
<u>11</u>	53	3	52	9
<u>Mean</u>	27.46	1 (mild)	14	7.5

4:1:4 Description of pedMIDAS results

Table 8 shows the individual sub domain scores for each participant who completed the pedMIDAS questionnaire. The mean pedMIDAS score in this population, 27.46, is lower than those given by the authors of the tool, which were 44.3(11). The mean pedMIDAS severity from these results therefore, is classified as mild, in contrast to the authors' mean score, which equates to a moderate pedMIDAS severity(11). The mean frequency of headache in this group was 14, higher than the mean given by the authors of the tool 9.5(11). Furthermore, the mean self reported migraine severity by this group was 7.5, again higher than the pedMIDAS authors' mean of 5.6(11).

4:2: Secondary outcome results:

Table 9: Food Cravings Inventory scores:

<u>Population</u>	<u>Total group</u>	<u>M</u>	<u>F</u>	<u>Age 5 - 12</u>	<u>Age 13-16</u>
<u>N</u>	12	4	8	3	9
<u>Total FCI</u>	2.55(0.31)	2.48(0.18)	2.74(0.58)	2.56(0.44)	2.5(0.3)
<u>FCI – high fat foods</u>	2.08(0.62)	2.25(0.13)	1.93(0.70)	2.10(0.26)	2.07(0.71)
<u>FCI - sweets</u>	2.67(0.76)	3.04(0.86)	2.48(0.64)	2.59(0.50)	2.71(0.88)
<u>FCI- carbohydrates</u>	2.75(0.76)	3.25(0.42)	2.50(0.62)	2.88(0.46)	2.69(0.76)
<u>FCI –Fast foods</u>	2.71(0.74)	2.75(1.19)	2.69(0.50)	2.81(0.55)	2.5(0.78)

4:2:1 Description of FCI scores

Table 9 shows the mean scores of the four food categories addressed by the FCI in the cohort studied. The overall mean scores of cravings for male and female migraineurs were above population normal comparisons. Male scores were 2.48 (population normal average 2.00), whilst female scores were 2.74 (population normal average 2.07)(126).

The results of food cravings for high fat foods show that male migraineur scores were substantially above average at 2.25 (average 2.00) whilst female migraineur scores were actually below population normal average at 1.93 (average 2.07)(126). No research has assessed mean food cravings inventory

scores in the paediatric population; there are no comparisons, therefore, that can be drawn from these findings.

Food cravings scores for sweets were higher in both males and female migraineurs than in comparison groups. Males scored 2.48 whilst females scored 3.04, both higher than comparison means of 1.92 and 2.17 respectively (126).

Cravings for carbohydrates were higher than average in both sexes. Male migraineur scores were 2.5, higher than the average of 2.13. Female migraineur scores were 3.25, much higher than controls of 2.31(126).

Cravings for fast foods were higher than average in both sexes of migraineurs. Male migraineur scores were 2.69 (average 1.97), whilst female migraineurs scores were 2.75 (average 1.85)(126).

Table 10: Child Behaviour Check List Scores:

Population	Total group	M	F
N	11	3	8
Internalising	7.91(3.83)	6.67(2.89)	8.38(4.2)
Externalising	14.9(7.46)	16.67(9.29)	15.5(8.6)
Withdrawn behaviour	2.91(2.21)	2.67(1.15)	3(2.56)
Somatic behaviour	1.64(1.2)	1.67(0.57)	1.63(1.41)
Anxious behaviour	3.36(2.5)	2.33(3.2)	3.75(2.3)
Delinquent	2(2)	2.67(2.3)	1.75(2.1)
Aggressive	14.5(7.9)	15.5(8.6)	13.3(4)

4:2:2 Description of Child Behaviour checklist scores

Table 10 highlights the average scores of the individual abnormal psychological traits addressed by the CBCL in the cohort studied. Male migraineur internalizing scores of 6.67 were below the average normal population scores of 7.5. Female migraineur internalizing scores, of 8.38, were above average for the normal population 8.1(212).

Male migraineur externalizing scores of 16.3 were higher than normal population comparisons of 11.9. Similarly, female migraineur externalizing scores of 15.5 were higher than normal population comparisons of 9.5.

Male migraineur withdrawal scores of 2.67 are higher than normal population comparisons of 1.9. Similarly, female migraineur withdrawal scores of 3 are higher than normal population comparisons of 2.

Male migraineur somatic scores of 1.67 are higher than male normal population comparisons of 0.8. Similarly, female migraineur somatic scores of 1.63 are higher than female normal population scores of 1.

Male migraineur anxiety scores were 2.33, lower than the male normal population scores of 4.9. Female migraineur anxiety scores were 3.7, lower than the female normal population scores of 5.2.

Male migraineur delinquent scores of 2.67 were marginally higher than normal population scores of 2.5. Female migraineur delinquent scores of 1.75 were marginally lower than normal population scores of 1.9.

Male migraineur aggression average scores of 15.5 are higher than normal population scores of 9.6. Similarly, female migraineur aggression average scores of 13.3 are higher than normal population scores of 7.6.

Table 11: Food Intake Questionnaire Scores:

Marker food	NUMBER OF FOODS IN GROUP	Overall (10)	Boys (3)	Girls (7)
Sugary	13	2.2(1.99)	1(1)	2.71(2.14)
Fatty	10	1.9(1.29)	2(1)	1.86(1.46)
Fibre	10	0.6(0.52)	0.66(0.58)	0.57(0.53)
Snacks	10	1.7(1.3)	1.33(1.53)	1.6(1.27)
Altered fats	5	0.9(0.1)	1(1)	0.86(1.21)
Low sugar	3	0.7(0.82)	1(1)	0.57(0.79)
Negative food marker	21	4.2 (2.34)	4(2.65)	4.71(2.21)
Positive food marker	21	2(1.75)	2(1)	2(2)

4:2:3 Description of FIQ Scores

Table 11 shows the mean scores of the different food markers addressed by the FIQ in the cohort studied. Male migraineur mean scores of sugary food intake were 1; substantially lower than normal population scores of 6.29(204). Similarly, mean female migraineur scores of sugary food intake were 2.7; substantially lower than normal population scores of 5.44(204).

Male migraineur mean scores of fatty food intake were 2; lower than mean normal population scores of 3.69(204). Similarly, female migraineur mean scores of fatty food intake were 1.86, lower than mean normal population scores of 3.24.

Male migraineur mean scores of fibre food intake were 0.66; lower than mean normal population scores of 2.54(204). Similarly, female migraineur mean scores of fibre food intake were 0.57; lower than mean normal population scores of 2.27(204).

Male migraineur mean scores of snack food intake were 1.33; lower than mean population scores of 5.86(204). Similarly, female migraineur mean scores of 1.6 were lower than normal population mean scores of 5.33(204).

Male migraineur mean scores of altered fats intake were 1.00; lower than mean population scores of 1.45(204) . Similarly, female migraineur mean scores of 0.86 were lower than normal population mean scores of 1.24. This could suggest that, in both sexes of the migraine population, intake of altered fat food was lower than their normal population contemporaries.

Male migraineur mean scores of low sugar food intake was 1.00; slightly higher than the mean population score of 0.9(204). Female migraineur mean scores of 0.57 were lower than the normal population mean of 1.8(204).

Male mean scores of negative food markers were 4; substantially less than the normal population mean of 10.02(204). Similarly, female mean scores of negative food markers were 4.71; substantially less than normal population means of 8.89.

Male migraineur mean scores of positive food markers were 2; less than the normal population mean of 5.73(204). Female migraineur mean scores of positive food markers were 2; less than in the normal population mean of 4.93(204).

Chapter 5: qualitative results of study:

5:1 Discourse on use of the psychometric tools:

A crucial finding from conducting the preliminary recruitment of this study has been assessing the utility of the different psychometric tools and the validity of the results they produce. There have been a number of issues in the use of these tools and it is important that these are reflected upon, particularly as some of these tools are widely used, without it being clear how extensively they have been validated. The following chapter will reflect upon the issues of each tool in turn.

5:1:1 PedMIDAS

The authors of this tool validated the tool themselves(11), but no other work has analysed its suitability as a tool to measure paediatric migraine disability. Question 1 asked, “How many full days of school were missed in the last three months due to headaches?” In some cases, participants firstly had to seek clarification of the question being asked; therefore, it could be argued that the question is not clear. Furthermore, the researcher’s explanation is based on his interpretation of the question, which is not infallible. Moreover, the researcher has to paraphrase the question and, in essence, is not asking the exact question shown on the questionnaire. Additionally, some participants admitted to simply being unable to accurately remember the exact number of days missed, so this question is open to recall bias. Often, participants would try to recall the full days missed in the previous month due to headache and merely multiply that number by three. This method is inaccurate in a pathology that waxes and wanes to the extent that migraine does. It is clear to see that there are issues of clarity and recall pertaining to the first question.

Question two asked “How many partial days were missed in the last three months due to headache?” As with the first question some participants needed clarification of this question. Again the researcher had to clarify by paraphrasing or giving an example e.g. “imagine your headache is so severe you can’t get out of bed in the morning and therefore go to school late” or

“you get a headache that is so painful in school you have to go home early”. This, again, is the researcher’s interpretation of the question. Another issue with two participants was that they had such severe headaches that they attended the medical sick room at school for a number of hours but then returned to the classroom. In the register, they will show as being in attendance at school but certainly were not in attendance at class. This ambiguity allows each researcher to interpret this individually and score accordingly; therefore, question reliability may be poor.

Question 3 asked “How many days in the last three months did you function at less than half your ability in school because of a headache?” Most children found it very hard to determine exactly if they were functioning at less than half their ability. Young children, i.e. 6 year olds, found this impossible to answer, whereas an adolescent found it easier to answer the question. Almost invariably participants knew when they felt unwell and remained at school, and remembered that they could not do work, but could not quantify, in certain incidences, if they were functioning at less than 50% of their ability. In this researcher’s experience it seemed that any incidence in which they felt even slightly unwell at school was counted as working at less than half their function, which in all probability is likely to be an overestimation.

Question four asked “How many days were you not able to do things at home (i.e. chores, homework etc) due to a headache?” This question posed particularly difficult problems. The majority of participants felt they did not do regular chores or homework so could not answer the question. The researcher offered other alternatives such as reading, playing computer games, or social networking. Participants felt they could relate better to these examples and offered a number of days on which they were unable to participate in these activities. It is unclear from the questionnaire, however, whether such substitutions of activity are allowed, or whether these jeopardise the validity of such a score. This is a limitation of the question.

Question five asked “How many days did you not participate in other activities due to a headache?” The response from participants was very good. The vast majority of participants felt they could clearly remember events which they had been unable to participate in, however, because they were

required to recall events from over three months ago it is still vulnerable to recall bias.

Question six asked “How many days did you participate in these activities, but function at less than half your ability?” Again the response to this question was positive from the majority of participants, because participants could remember the disappointment of not being able to enjoy the event in which they were taking part. Once more there is limitation of recall bias over the last three months.

It is clear to see that there are some issues when using the pedMIDAS to assess headache disability, which is somewhat surprising discovery given that it is used widely for this purpose, for example it is currently being used in a national migraine treatment RCT (which is pharmaceutically sponsored) in the U.K(47). Ideally the questionnaire should be validated objectively (i.e. by scorers who are not the authors of the tool) again, for there are issues, particularly the wording of questions, which require revision to improve its usability and reliability.

5:1:3 Dutch Eating Behaviour Questionnaire:

The Dutch eating behaviour questionnaire has been validated a number of times and is a widely used tool for assessing appetite behaviour of children age nine to sixteen. It is a thirty three-item questionnaire. The rating score is: never; rarely; sometimes; often; very often. Participants understood the vast majority of questions and they responded appropriately, however, a few questions needed clarification. Question 3 asked “Do you have a desire to eat when you have nothing to do?” Many of participants asked whether “having nothing to do” meant when they were bored? The researcher assumed this was the meaning of the question and responded in the affirmative to this question, but this is open to interpretation. It may be better for the question to ask, “Do you have the desire to eat when you are bored?”

Question 9 asked “If you see or smell something delicious, do you have a desire to eat it?” A large number of participants asked whether the question implied immediate consumption or consumption in the near future e.g. within an hour? This author did not know the correct answer to this question and

assumed that the question in the tool implied immediate consumption. Most participants felt that provided it was a certainty that they would not lose the opportunity to eat the treat unless they ate it immediately, they could refrain from eating for an hour or two if they knew it was being served soon. Question 9 needed to be more specific, because if it meant eating immediately or not at all, the results might be considerably different.

The other questions were answered without issue, highlighting that the DEBQ is a very useable questionnaire in this cohort of patients. One issue, as with any utilization of a Likert scale, is that participants tried to answer the questions as if the options were 'yes' or 'no', giving no consideration to degrees of scaling. Even with continual reminder of the true options they reverted back to 'yes' or 'no' and, it is possible that participants use the extreme ends of the scale as proxy for affirmative or negative responses. This could result in invalid polarised results i.e. taking option one 'never' to mean 'no' and option 5 'very often' to mean 'yes.'

5:1:4 Child eating behaviour questionnaire:

This questionnaire consists of 35-items. The rating score is never (1), rarely (2), sometimes (3), often (4), always (5). This questionnaire is very well designed. It is a parent proxy report tool of a child's eating. Testament to its robust design is the fact that no participants' parents had major issues in answering the questions. The only question that caused particular issue was question 28, which focuses on food reward. Parents are asked to agree or disagree with the statement "Even if my child is full up s/he finds room to eat her/his favourite food". This caused confusion to a number of participants' parents. They were unsure whether the food that had made their children full up was also their favourite food or an alternative less pleasurable food. This is important because parents felt that if the food their children had just consumed was their favourite food, e.g. cake, they would be less inclined to find room for more of it, but if it were a food such as a savoury meal such as roast dinner, that had just been consumed, they would be far more likely to make room for their favourite food. This question needs clarifying by the authors. It was assumed that it inferred the latter scenario

and scored accordingly. The ambiguity of this question is a minor limitation of this questionnaire.

A particular strength of the CEBQ design is that a number of the questions are 'reverse scored' i.e. the strongest agreement to a question results in the lowest score. The importance of reverse scoring is crucial to this questionnaire; it forces the participant to give due consideration to the question, and discourages response acquiescence. In this researcher's experience, the participants were seen to give greater consideration to questions asked and the answers given than they might do with other psychometric measures.

5:1:5 Food intake questionnaire:

This questionnaire is an epidemiological tool that records whether certain foods have been eaten on the previous day. It has been used extensively for this purpose; one particular study has previously assessed eating habits of 40,000 children in Liverpool(206). This questionnaire had the best usability in preliminary data collection from this study. The questions are very straightforward and easy for the participants to interpret e.g. "Yesterday, did you have anything at all to eat or drink before leaving home to come to school?" The responses required were affirmative or negative, rather than the graded Likert scale. Furthermore, the questions were easy to ask and answer, so the questionnaire took very little time. This is an important feature of the tool because if the questionnaire is lengthy participants become inattentive and the reliability of their answers may come into question. This questionnaire suitably captured a general description of food intake in paediatric migraineurs, however, there were still a few minor issues, one of which was recall bias, but it should be remembered this plagues all memory-based questionnaire. A further issue was that if patients were recruited on a Monday or on a half term holiday, some of the questions were not applicable to the previous day e.g. 'did you eat a school lunch (yesterday)?' The participant was forced to think back to the last day at school, thereby introducing greater recall bias. If the day of recruitment was at the tail end of a weeklong holiday recall could be a big limitation. Systematic bias occurred when parents would contradict the child's answer. It is unclear in such

circumstances whether the parent is over reporting positive markers of food or whether there has been a genuine lapse of memory on the part of the child. This finding is probably idiosyncratic, because in previous studies the child completed the FIQ in the absence of their parents/carers. Furthermore, this researcher asked participants the questions verbally for sake of expediency. Whether this had effect on results is unclear. The participant usually anonymously answers the FIQ in written format and this may be a reason why there is such underreporting. This of course questions the validity of the tool in this study, it being used in such a contrasting way from the authors of the tool. Another limitation of the tool is that older children may have underreported negative foodstuffs, being aware what constitutes a healthy diet. This is therefore a potentially social desirability bias of the tool. Overall, this questionnaire was the most useable, capturing food intake in this paediatric migraineurs, but a few limitations still existed.

5:1:6 Food cravings inventory

This questionnaire is a 28-item questionnaire to assess what types of food migraine patients generally crave i.e. their trait food cravings. Participants had to rate to what extent they craved certain food on a Likert scale. Options were: 'never', 'rarely', 'sometimes', 'often' and 'always'. This questionnaire was easy to use. Participants responded well to the options, with no confusion, or the need for clarification, however the questionnaire had to be altered somewhat for our purposes. At the beginning of the questionnaire a definition of cravings was given as "an irresistible urge to consume a specific food(200)" Although the researcher quoted this definition, because the study was interested in trait food cravings, not state cravings (which have already been informally looked at(151)) a caveat was added, that participants should apply this to everyday living, not specifically around the time of their headaches.

Alterations to a few of the foodstuffs had to be made. Cinnamon rolls were changed to swiss rolls, corn bread to crackers, and chips to crisps. This was not clarified with the authors of the tool and as such is a limitation of the study. However, this was a necessary change to avoid confusion in this setting.

There were no other issues with this questionnaire and it was very useful at elucidating food cravings in this cohort.

5:1:7 Child behaviour checklist

This parent-reported psychometric measure assesses emotional and behavioural problems in children aged 4-18 years. The first part concerns social skills, participation in organizations, contact with friends, participation and skills in sports and academic performance ratings. This section proved particularly taxing. Section one asks parents to name three types of sport their child likes to take activity in. In the majority of cases parents reported that their children had very few sports that the child liked to take part in, naming one or less in the majority of cases. This is an interesting finding. It may suggest that paediatric migraineurs take part in less physical activity than migraine free peers. Reflecting upon the potentially alternative mechanisms in the obesity and migraine relationship (chapter 1.2.5) this is an important qualitative finding. This may be a preliminary finding that migraineurs have reduced exercise levels, placing them at increased risk of obesity. Alternatively, all children in Liverpool may do less exercise than other parts of the United Kingdom. Or potentially, as discussed in chapter 1.2, it may simply be that sedentary activities are increasingly replacing active hobbies in the entire paediatric population.

Section two asks parents to report three of their child's interests/hobbies, *excluding* radio, TV and computer. The majority of parents reported children had few hobbies other than computers or TV, and so few parents could name three hobbies. Section three asks parents to name up to three organized clubs their child belongs to. Again, the majority could name a maximum of one club, possibly due to the lack of activities available for children in the geographical area. Alternatively, it may be that migraine causes general inertia and aversion to activity. Or, the recent advent of social networking on personal computers might be thwarting activity. There are a plethora of reasons for such findings, but, irrespective of the cause, it led to leaving the questionnaire incomplete.

A limitation of the study was the presence of the child when parents were completing the section pertaining to the academic performance of that child, because it is plausible that parents would over-report the academic ability of the child. Equally, a sub section asks parents to report concerns over their child; it is possible they would underreport such issues.

The second part of the questionnaire deals with emotional and behavioural problems classified as internalized or externalized (full explanations of which are in the chapter 4:2:6). Parents answer on a 3-point Likert scale to indicate how representative the items are of the child's behaviour during the preceding six months. As above, it is possible the parents underreport poor behaviour such as 'temper tantrums' or 'cruelty, bullying or meanness to others', due to the presence of the child in the room.

It is a fault of the study design that children are present whilst parents answer the tool, but it is very possible that this it reduces the validity of the answers. In addition to this, the tool takes 20 minutes to complete, the same length it takes to complete all the others combined. From this preliminary data it can be deduced that the CBCL was laborious to utilise because of the length of time it took to complete. It is however, widely used in both paediatric research and paediatric clinical practice.

Chapter 6: Discussion

6:1 Discussion of results:

In the course of this research formal assessment of various appetite behaviours, food cravings, food intake and psychological behaviours have been carried out in a paediatric migraine population. Unfortunately, due to a number of limitations of this study, discussed in detail in chapter 6.4, it is difficult and inappropriate, to draw firm quantitative conclusions from the study's findings.

The sample size of these results must be highlighted, in order to put these results into perspective. The results in chapter 5 are preliminary; there is acute awareness that the study is at a nascent stage and that for more meaningful conclusions a greater sample size is needed.

What can be gleaned from the early stages of this pilot study is that a successful comprehensive literature search was achieved. Furthermore, a great deal about the feasibility of the study design, and in particular the suitability of the relevant psychometric tools, has been learnt. This warrants further discussion.

With regards to the study design, there are a couple of issues. Although the ethical approval delay was the main rate-limiting factor in recruitment of participants, once ethical approval was gained recruitment was slower than anticipated. This was due to the necessary inclusion criteria that participants were migraine medication naïve. This inclusion criteria is an advantage of the study. As mentioned in chapter 1.1.9, prophylactic migraine medications can alter weight and presumably appetite behaviour. Therefore drug naïve migraineurs were essential. Furthermore, by recruiting newly referred migraineurs the study is capturing participants at an early stage of their migraine trajectory. Cases of migraine are generally referred when the severity of migraine is at a point that it warrants specialist intervention. Therefore this inclusion criteria aimed to capture a population of migraineurs at the same point in their trajectory of a chronic disease. Comparing this to the methods employed in the previous studies reviewing the migraine and

obesity relationship (chapter 3), this is a novel, advantageous component of this study design. In potential further prospective study, this inclusion criteria will be crucial in trying to elucidate causation between migraine and obesity.

It was surprisingly laborious to recruit control participants for the study. In the original design of the study, a control arm was not integral to the design, since the focus was on the association of appetite behaviour and migraine, and the analysis would focus on this. The study aimed to map appetite behaviour of migraine patients. There are normative data values that exist for the general population for the relevant measures, although not always of the exact same age group. Therefore a control arm of the study could be continued until completion, but is not essential to the study.

With regard to the psychometric tools used in the design, there are a number of issues as highlighted in the qualitative results that need addressing.

There were some issues with the pedMIDAS tool. Firstly, with regards to the clarity of its questions and that its design potentially lends to recall bias. Furthermore, the suitability of its questions to its proposed demographic was suboptimal. The tool has not been independently validated. Reflection upon whether the pedMIDAS accurately addresses migraine severity and, therefore, whether it is suitable for the purposes of this study, must be considered.

Secondly, there were minor issues with DEBQ tool. There was lack of clarity in a couple of the questions. There was also an issue that participants gave polarised results on the Likert as a proxy for affirmative or negative responses. Although not utilised in the inception of the recruitment, the DEBQ-C overcomes this issues by being a three-point scale, reducing patient acquiescence in answering. Overall, however, the DEBQ was a very useable tool. Therefore with a couple of minor recommendations this tool is suitable for continued use in the study design. It is notable that the DEBQ has been widely used in previous studies to assess appetite behaviour. In previous work the DEBQ subscales have been utilised in neuro-imaging studies which associated certain appetite behaviours with neurotransmitter release(213). In potential further research the DEBQ may be able to be mapped with neuro-

imaging of migraineurs.

Similarly, the CEBQ was an easily utilised tool. Again, there was an issue with the clarity of a couple of the questions in the tool. The tool did, however, address the relevant appetite behaviours. Furthermore, the 'reverse scoring' element of the tool is a particular strength, leaving it less vulnerable to participant acquiescence than the DEBQ. After addressing the minor problem of clarity of a couple of the questions in this tool, it will be suitable for continued use in the study design.

The FIQ was utilised in a different fashion from that intended by its authors. Firstly, questions were asked of participants verbally. Previously the tool was administered for the child to record results on paper. Secondly, parents were in attendance when the participant was answering questions. Previously, the participant answered the tool in the absence of their parent/carer. Thirdly, the tool had previously been administered to a much larger number of children e.g. over 700 patients in one study(205). Fourthly, the tool had previously been administered to children over 10 years old. This is important because it is possible that children at the younger end of the age spectrum would fail to fully understand the questions asked of them in the tool. Therefore reflection about the tools suitability in the study and, subsequent recommendations are merited.

The FCI was an easily utilised and illuminated food cravings in the preliminary migraine population studied. It has been previously successfully used in different demographics, from normal weight subjects to obese subjects with mood disorders(126, 214). Therefore it is suitable for use in the continued study.

The CBCL was very laborious to use, due to the length of time it took to complete (20minutes). Additionally, the tool was utilised in the presence of the child; in previous studies it is utilised in the absence of the child. These issues deserve reflection in the recommendations section for the continued study.

Chapter 6:2: Recommendations:

The research performed by this author has failed to show any significant statistical findings. Current results cannot confirm whether or not migraine is associated with aberrant appetite behaviours at this preliminary stage. There were, however, qualitative findings about the rigor of the methodology of the study, in particular the applicability of certain psychometric tools. These issues must be dealt with to improve the continuation of this study. Furthermore, there are a number of different avenues that could be exploited to further research in this area.

For firmer conclusions to be drawn about the relationship between migraine and appetite behaviours, it is imperative that this study is continued. With the study having achieved full ethical and site-specific approval, and producing preliminary results, the full pilot study of 90 patients (60 cases and 30 controls) should be conducted. From the results, a larger scale study should be conducted on a 900 participants.

Chapter 6.2.1: Adaptations to study design

Migraine severity measurement tool:

The pedMIDAS tool had a number of limitations as highlighted in the discussion. To ensure that migraine severity is accurately recorded in the continuation of the study the following issues must be addressed. Discussion about the potential recall bias also needs to be addressed. Potential alternative methods of measuring migraine severity are migraine diaries and calendars. A number of migraine diaries have been designed(215), and applied in a number of settings, from scientific research to drug trials. They require the migraineur to record a number of details of each migraine attack e.g. length of attack, pain etc. The advantage such tools have are that they reduce recall bias, a key problem with the pedMIDAS. One study highlights that psychometric tools measuring severity of migraine overestimate its severity compared to migraine diaries(216). Migraine diaries are, however, more labour intensive for the participant. Furthermore their success depends on the diligence of the participant in completing the diary or calendar. Moreover, if applied to this study, they would necessitate a further meeting

with the participant, entirely altering the recruitment process. Another alternative option would have been to replace the tool with an equivalent i.e. the HIT-6 questionnaire. A potential problem with replacing the pedMIDAS with another migraine severity tool, that has not been first utilised in preliminary studies, is that it may have an equal amount of limitations that will hinder the validity of the large-scale study. Therefore, due to the nature of the study, which is a pilot study with expedient recruitment design, a diary is not warranted for the study, even if it is the zenith of migraine severity prediction. Furthermore, it would be foolish to blindly replace one psychometric tool that measures migraine with another, particularly as the HIT-6 tool is designed to measure adult migraine. Furthermore, the pedMIDAS, for all its limitations, is a tool that has been used widely in international studies. Therefore, overall, after addressing the issues of the pedMIDAS tool, it should remain the primary outcome measure for predicting migraine severity for the reasons highlighted above.

Appetite behaviour measurement tool

As highlighted in the discussion, both the CEBQ and DEBQ tools were useable and had good face validity in mapping appetite behaviours. Therefore they should continue to be used as the tools to assess appetite behaviour in this study. It would be beneficial to clarify with the authors of the DEBQ the issue of ambiguity over question 3 and question 9. Similarly it would be beneficial to contact the authors of the CEBQ about the issue of ambiguity over question 28 (“Even if my child is full up s/he finds room to eat her/his favourite food?”). Carers were unsure whether the food that had satiated the participant was also their favourite food or not, because this would alter the answer given. It would be useful to discuss how to record answers when two parents give conflicting scores in the CEBQ, as occurred a couple of times in preliminary recruitment. In spite of these minor issues, the DEBQ and CEBQ should remain the appetite behaviour tools in the continued study. The disparity between the preliminary scores obtained from the DEBQ and the CEBQ was surprising. Many of the questions focus on an overlapping concept e.g. external eating behaviours. This highlights the importance of having a self-reported tool and parent-reported tool because, although only very preliminary results, it is already shown there is a difference in

perception of appetite behaviour between the two. It is crucial that both tools are kept in the design for the entirety of the study, to highlight if these differences remain in a bigger population. None of the average score results were statistically significant, therefore, robust conclusions on the disparity between the CEBQ and DEBQ cannot be drawn. For the full study, however, it will be important to keep both the DEBQ and CEBQ in the study design to see if, with a large sample size, the results become more consistent with one another. It would be useful, once the study is complete, to correlate individual items of each tool to assess if there is any relationship between their constructs. The authors of the CEBQ have supported this idea.

An alternative way of measuring appetite behaviour would be to have utilised ingestive laboratory studies. The University of Liverpool has a group known as the Liverpool Obesity Research Network (LORN); who regularly study participants' appetites in a number of ingestive laboratory settings(217, 218). Theoretically, studying migraineurs trait appetite behaviours in this way would be a more direct measurement of appetite. Comparable appetite constructs assessed in appetite psychometric tools can be measured in these laboratories e.g. satiety responsiveness; by feeding subjects to supposed satiation and then offering a further highly palatable food to assess if they continue to eat. There are a plethora of different appetite constructs assessed in ingestive laboratories, beyond the remit of this thesis. This type of assessment of appetite behaviour is direct, being less prone to limitations (mentioned above) of a psychometric tool. This type of study would, however, be far more demanding on the participant and more costly. Therefore for the pilot study this was unfeasible. This methodology of appetite assessment is worth due consideration for future study in this area.

Reflecting on the qualitative results of the CBCL questionnaire, these results showed that this tool was a laborious one to use, taking twenty minutes to complete. Moreover, due to the study design, whereby participants were present whilst parents/carers answer questions about the participant's behaviour, the validity of scores are called into question. Consequently, parents/carers should be asked the CBCL questions without the participant present. The CBCL is a well-established tool in assessing paediatric psychological traits. Therefore although it is time consuming, no

parent/carer actually refused to answer the tool due to the length of time it took to complete. Furthermore, this tool has been used in a number of previous studies to assess the behaviour of migraineurs, consistently highlighting that migraine sufferers have higher internalisation scores(219, 220). Therefore, because it has been so widely used in migraine patients, and yielded consistent results, although it is laborious to use, it should remain in the study but with the above recommendation.

The preliminary FIQ scores suggested underreporting across all of the domains of the tool. As mentioned in the discussion, the tool was utilised in a different manner from that intended by its authors, which may be a reason for the underreporting; equally the sample size may be the cause of this. The tool has been used extensively before successfully, therefore it is recommended that the tool is included in the study with the following changes: Firstly, the participant completes the tool by hand (not verbally). Secondly, the participant is not in the presence of the parent when completing the tool. Practically, when the parents/carers need to answer the CBCL the child could enter another room supported by clinic nurse and fill out the FIQ. This will make the recruitment phase more efficient. This is feasible because in the preliminary recruitment of the study the clinic nurses were available and supportive of aiding recruitment. A much larger sample size is necessary to glean meaningful results for the FIQ. It is unclear what samples size is needed because it is being used in a novel area. As such, it is recommended to continue to be used in this study until completion with the above recommendations.

As highlighted in the discussion, the FCI was useable and accurately focused on food cravings. For continuation of the study, the tool should remain in the study design. Contact with the authors of the tool should be made to discuss the replacement of certain American foodstuffs with British equivalents, to ensure consistency is up kept when utilising the tool.

Recruitment was slower than predicted, mainly due to the inclusion criteria that participants must be new patients who were migraine medication naïve. For the successful completion of the study it will be imperative to increase the potential recruitment population size. As previously designed, the most

feasible way of managing this is to recruit participants from the general paediatric clinic. Although this avenue was previously unfruitful due to another planned concurrent migraine study (which has still yet to commence), potentially this may be readdressed. Since the end of recruitment for this MPhil, a research nurse has been appointed for the alternative migraine study. Within their study design is the aim to recruit from the tertiary paediatric migraine clinics as well as general paediatric clinics. Therefore, pragmatically, it is feasible that strong collaboration between the primary investigator of this study and the research clinic nurse would result in a larger recruitment population. To catalyse this, a further meeting between the general paediatric consultants, neurology consultants, the research clinic nurse and the primary investigator is needed to readdress this issue. If this remains an unfruitful avenue, potential alternatives are possible. Recruitment from another paediatric hospital in the region is possible. Both St Helens and Knowsley Teaching Hospitals NHS Trust and Wirral University Teaching Hospital have paediatrics units that manage migraine. Therefore, with amendment to the both the study design and ethics application to make the study multi-centre, this would be very likely to improve recruitment rates. One logistical issue with this option is that there is not funding in the study for another study recruitment officer, therefore it may be unfeasible for the primary investigator to work between two sites. Considering, however, that recruitment was not occurring every day at the current site then it may be the most pragmatic option.

The control arm of the study, whereby there are thirty non-migraine participants, was strongly suggested by the statistician when designing the study. This was not part of the preliminary study design. The recruitment of control participants was more arduous than migraine participants. Migraine is the most common referral to the paediatric headache clinic at Alder Hey Children's NHS Foundation Trust. More generally, migraine is more prevalent than other types of paediatric headache e.g. tension type headache(221). Therefore this is a key reason why it was hard to recruit control participants. Considering this, and that there are data norms for each of the psychometric tools, it is recommended to recruit only migraine participants into the pilot study for the continuation of the study.

6.2.2 Further potential research

There is room for further research in this area. As mentioned in chapter 1:1, many migraine medications affect the weight of their users. Pizotifen, a very commonly used prophylactic migraine treatment, has been shown to cause weight gain (45, 50, 53). Conversely, Topiramate, another prophylactic migraine medication, has been shown to cause weight loss(36). Potential further research could be the design of a longitudinal study that assesses the weight, appetite behaviours, migraine severity, food cravings and food intake of migraine participants on these migraine medications. Theoretically, at baseline, i.e. when participants are prescribed the relevant prophylactic medication, participants could answer the psychometric tools from this study design. Developments could then be followed up at 6 months and 1 year, reassessing the aforementioned parameters at each stage. Such a study would highlight whether particular appetite behaviours have a role in weight change. It would be useful to assess whether participants' migraine severity is associated with changes in weight. Based on this author's current hypothesis, it could be postulated that with Topiramate, which can cause weight loss, the participant's migraine severity and hypothetical aberrant appetite behaviours are reduced. Conversely, it could be postulated, that with the use of Pizotifen, which can cause weight gain, the patient's migraine severity and hypothetical aberrant appetite behaviours worsen. This is a novel concept that, hitherto, has not been studied. Such a future study may have wider implications for the choice of pharmacological therapy for management of migraine.

Another aspect of this further study, or even a separate study would be to assess the exercise levels of paediatric migraineurs. The type of measurements and their respective degrees of accuracy in measuring exercise vary. Self-report questionnaires to assess number of participant activities, and parental perception of their child's exercise levels have previously been designed and utilised(96, 222). Objective assessment of migraineur activity could be obtained by utilising accelerometers for participants to wear for a fixed period e.g. seven days (223). Alternatively, isotopes have been utilised to assess energy expenditure in subjects(224). Both of the latter methods would be more costly and require more specialist input than a self-report

questionnaire. They may, however, offer greater insight into the activity levels of migraineurs. Irrespective of the eventual methodology chosen to assess exercise, considering that potentially exercise could mediate the relationship between migraine and obesity (see chapter 1.2.5) and, is hitherto not been studied, this is a worthwhile aspect of study for the future.

Potential further research in this field could be a population based study correlating primary headache with obesity and headache with diet. A very large cohort of children, 13,971 in total, have been monitored since in utero in a study called “The Avon Longitudinal Study of Parents and Children (ALSPAC)(225)”. This prospective longitudinal study of this cohort assesses all of life data (data from birth and annually hereafter), but is particularly interested in the anthropometry of these children over time.(226) Throughout the study, details of children’s weight, BMI, waist circumference, and Dual–Energy X-Ray Absorptometry (DXA) measurements of total and regional fat mass, are recorded at regular intervals(227). There is also detailed data on diet in this study, recorded at 3, 7 and 12 years old, utilizing a food frequency questionnaire on the latter two occasions (227). The study has also measured primary headache frequency at regular intervals. Ultimately, it would be interesting to collaborate with the authors of this study and exploit such a rich volume of data, the largest longitudinal data on paediatric headache in the U.K. If successful collaboration occurs, correlation of headache with weight and headache with diet on a population based scale can be conducted; a novel design that has not been conducted in the British paediatric population. Based on previous work the hypothesis would be that increased severity of migraine is associated with increased weight. More importantly, because data have been collected since the birth of participants and it is a longitudinal study, causation between the migraine and obesity relationship could potentially be elucidated.

6:3 Implications of the study:

The implications of the quantitative results of this study are very limited due to the limited sample size of the study thus far. There is not a strong enough body of results to suggest the need for a change in clinical practice. It is possible, however, to envisage that if further investigation found positive association between migraine and appetite, that there could be a number of implications for clinical practice.

Children who are overweight in youth are at increased risk of being overweight in adulthood(69, 228). The consequences of being overweight are discussed in chapter 1.2. Theoretically, if it is identified in further study that migraineurs are at increased risk of increased adiposity, the implications are multiple; from simple implications such as increasing the frequency of a child's BMI measurement in migraine clinics, to ensuring all paediatric neurologists give greater attention to the weight and appetite of their migraine patients.

There are a number of behavioural methods(134, 229) that could potentially be very useful at ameliorating the effects of aberrant appetite behaviours. As the current study has no robust conclusions from the association between appetite behaviour and migraine, these potential implications are merely postulations.

More immediately, the body of work so far has implications for the experience of recruitment and utilising the psychometric tools in this preliminary work. Adopting the recommendations the study design should become more robust, and hence the full pilot study results gleaned should be reliable. Once the study is completed, it will be more appropriate to determine implications of the study.

Chapter 6:4 Limitations of the study or study design:

6:4:1 Application for ethical and site-specific approval

There are a few factors that limited the potential to draw rigorous conclusions. The largest rate-limiting factor of undertaking this study was the process of gaining ethical and site-specific approval for the study. The hypothesis and study design were only conceived subsequent to the inception of the MPhil. Accordingly, the first few months were spent immersed in literature reviews and protocol design (with multiple iterations). The primary investigator was informed to apply for site-specific approval prior to applying for local ethics research committee approval and the application for site-specific authorization was finalized in January 2009. The process of site specific application involves applying to the R&D department with all relevant documentation, which is then referred to the primary reviewer and expert reviewer (from the relevant field of interest) who oversee the study. The reviewers then suggest changes to the study and further review the amended study design and, if of acceptable standard, the R&D committee reviews the application, comprised of ethicists, clinicians, statisticians and researchers, at the next available monthly meeting. There was significant delay by the R & D department in assigning the study a primary and expert reviewer. In mid February, after further liaison with the R&D department, it was decided that the study would not be reviewed in time for the next meeting, therefore delaying the review until late March. For unknown reasons the March meeting was subsequently cancelled by the R&D department. The primary investigator decided to discount the advice given by R&D not to simultaneously apply to the Local Ethics Research Committee, so that both applications would be completed in the same timeframe and the study could be commenced. Two reviewers were assigned to the study by the R&D department in very late March, therefore by the time the reviewers had given suggested changes the study could not enter in April R&D committee meeting. In the interim, this author attended the Local Ethics Committee review meeting and, achieved ethical approval subject to minor amendments (ref number: 09/H1017/51). The study was finally reviewed by the R&D department in early May and was given conditional

approval, subject to a few very minor adjustments. As a result of the aforementioned delays, the recruitment of the study did not start until the beginning of June.

It is unclear whether this process of site-specific approval was abnormally prolonged, or whether it was shortsighted to undertake a project from a nascent stage in the one-year timeframe. Irrespectively, this process is a large limitation of the study. There are two potential solutions to this large limitation. Firstly, for robust conclusions to be drawn about the study's hypothesis, the study needs to be continued until completion, as originally envisaged. Secondly, for this study to be completed in this last year, application for ethical and site-specific approval should have been obtained prior to the commencement of the MPhil. These unexpected setbacks have taught the author a large amount about rigorous study design and research applications; a valuable, transferable skill.

6:4:2 Limitations of the recruitment process

As mentioned in the study design, a key part of the inclusion criteria was to recruit only newly referred migraine patients who were drug naïve. The concept behind patients being new referrals was that these migraineurs should, in theory, have a relatively new diagnosis of migraine sufficiently severe for specialist referral, or have had a progression to a more severe migraine warranting specialist referral. Recruiting this type of migraine patient ensured that the study encompassed a group of migraine patients with the most severe migraine, i.e. more aberrant neurobiology. Previous work on migraine and obesity has shown that it is at the more severe end of the migraine severity spectrum that there is a relationship with obesity (44). Reflecting upon this, and the neurobiology review in chapter 2.2, recruiting this group of severe migraine sufferers would mean this population would be most likely to express aberrant appetite behaviour.

The concept behind participants being drug naïve was that, many of the migraine treatments, namely Topiramate and Pizotifen, cause overt weight change (as highlighted in section 1.1) potentially through disruption of normal appetite behaviour (though this has currently not been studied). It was therefore important that any newly referred patient who had been

prescribed any such medication was excluded from the study.

Unpublished internal figures suggest that there are ten new migraine referrals per month at Alder Hey. Less than 50% of potential participants were recruited into the author's study. To counter this problem, extensive efforts were made to build a relationship with general paediatricians at Alder Hey hospital, who deal with a smaller, but still substantial number of migraine referrals. After a number of preliminary meetings it became clear this avenue was obstructed by a concurrent large multi-centre randomized control trial into migraine (173).

With the aforementioned issues surrounding ethical approval, combined with the issues in recruitment, due to necessarily rigid inclusion criteria and poor recruitment response rate, these factors greatly limited the potential of the study.

6:4:3 The potential bias of a hospital clinic based study

A second limitation of this study's design, from an epidemiological point of view, is that the study population is recruited from a tertiary clinic. Firstly, clinic based studies of co-morbidity are vulnerable to overestimating the condition due to a phenomenon known as Berkson bias(230). Any two conditions may occur at higher frequency at clinic due to consultation or referral, therefore, an indefensible criticism of the study design is that it could potentially overestimate aberrant patterns of appetite.

Similarly, it is likely that many of the migraineurs who attend tertiary clinics are those at the most severe end of the migraine spectrum in terms of headache-associated disability. Those with the greatest impact on their life due to migraine are those most likely to seek specialist care, or be referred to a specialist. It could, therefore, be argued that, by focusing on a population of severe migraineurs, that this is not a true representation of the general population of migraine sufferers; findings of aberrant appetite behaviours in this severe migraine population might not, therefore, be representative of the general migraine population's appetite behaviours.

Although both of these criticisms of a clinic-based population are fair, it is equally fair to suggest that a clinic-based population is suitable for a pilot

study of a novel hypothesis. For firm conclusions on the relationship between migraine and appetite to be made, a population-based study will be necessary. For a pilot based study, aiming for preliminary findings in appetite behaviour of migraineurs, a clinic-based population is more feasible, both fiscally and for recruitment purposes.

6:5 Conclusion:

Drawing robust conclusions from this study is not possible. Ultimately, the sample size of the results prevents definitive insights into the relationship between migraine and appetite behaviour. There are however, some interesting preliminary results about the study design and tools of the study. The recommendations chapter (section 6.2) highlights the necessary changes to improve the study in response to the qualitative findings, in order that robust quantitative findings can be elucidated when the study is continued to completion.

1.1 Migraine without aura

Previously used terms:

Common migraine, hemicrania simplex

Description:

Recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Diagnostic criteria:

- A. At least 5 attacks¹ fulfilling criteria B-D
- B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)^{2;3;4}
- C. Headache has at least two of the following characteristics:
 - 1. unilateral location^{5;6}
 - 2. pulsating quality⁷
 - 3. moderate or severe pain intensity
 - 4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)
- D. During headache at least one of the following:
 - 1. nausea and/or vomiting
 - 2. photophobia and phonophobia⁸
- E. Not attributed to another disorder⁹

Notes:

- 1. Differentiating between 1.1 *Migraine without aura* and 2.1 *Infrequent episodic tension-type headache* may be difficult. Therefore at least 5 attacks are required. Individuals who otherwise meet criteria for 1.1 *Migraine without aura* but have had fewer than 5 attacks should be coded 1.6.1 *Probable migraine without aura.*
- 2. When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.
- 3. In children, attacks may last 1-72 hours (although the evidence for untreated durations of less than 2 hours in children requires corroboration by prospective diary studies).

4. When attacks occur on ≥ 15 days/month for >3 months, code as 1.1 *Migraine without aura* and as 1.5.1 *Chronic migraine*.
5. Migraine headache is commonly bilateral in young children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.
6. Migraine headache is usually frontotemporal. Occipital headache in *children*, whether unilateral or bilateral, is rare and calls for diagnostic caution; many cases are attributable to structural lesions.
7. *Pulsating* means throbbing or varying with the heartbeat.
8. In young children, photophobia and phonophobia may be inferred from their behaviour.
9. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

1.1 *Migraine without aura* is the commonest subtype of migraine. It has a higher average attack frequency and is usually more disabling than 1.2 *Migraine with aura*.

Migraine without aura often has a strict menstrual relationship. In contrast to the first edition of *The International Classification of Headache Disorders*, this edition gives criteria for A1.1.1 *Pure menstrual migraine* and A1.1.2 *Menstrually-related migraine*, but in the appendix because of uncertainty over whether they should be regarded as separate entities.

Very frequent migraine attacks are now distinguished as 1.5.1 *Chronic migraine* provided that there is no medication overuse. Migraine without aura is the disease most prone to accelerate with frequent use of symptomatic medication, resulting in a new headache which is coded as 8.2 *Medication-overuse headache*.

Regional cerebral blood flow shows no changes suggestive of cortical spreading depression during attacks of migraine without aura although blood flow changes in the brainstem may occur, as may cortical changes secondary to pain activation. This contrasts with the pathognomonic spreading oligoemia of migraine with aura. In all likelihood spreading depression is therefore not involved in migraine without aura. On the other hand the messenger molecules nitric oxide (NO) and calcitonin-gene-related peptide (CGRP) are clearly involved. While the disease was previously regarded as primarily vascular, the importance of sensitisation of perivascular nerve terminals, and the possibility that attacks may originate in the central nervous system, have gained increasing attention over the last decades. At the same time the circuitry of migraine pain and several aspects of neurotransmission in this system have been recognised. A significant contribution has been made by the advent of the triptans, 5HT_{1B/D} receptor agonists. These drugs have remarkable efficacy in acute attacks and, in view of their high receptor-specificity, their mechanism of action provides new insight into migraine mechanisms. It is now clear that migraine without aura is a neurobiological disorder and clinical as well as basic neuroscience currently advances our knowledge of migraine mechanisms at an increasing speed.

1.2 Migraine with aura

Previously used terms:

Classic or classical migraine, ophthalmic, hemiparaesthetic, hemiplegic or aphasic migraine, migraine accompagnée, complicated migraine

Coded elsewhere:

13.17 *Ophthalmoplegic "migraine"*.

Description:

Recurrent disorder manifesting in attacks of reversible focal neurological symptoms that usually develop gradually over 5-20 minutes and last for less than 60 minutes. Headache with the features of migraine without aura usually follows the aura symptoms. Less commonly, headache lacks migrainous features or is completely absent.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criterion B
- B. Migraine aura fulfilling criteria B and C for one of the subforms 1.2.1-1.2.6
- C. Not attributed to another disorder¹

Note:

- 1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

The aura is the complex of neurological symptoms that occurs just before or at the onset of migraine headache. Most patients with migraine have exclusively attacks without aura. Many patients who have frequent attacks with aura also have attacks without aura (code as 1.2 *Migraine with aura* and 1.1 *Migraine without aura*).

Premonitory symptoms occur hours to a day or two before a migraine attack (with or without aura). They include various combinations of fatigue, difficulty in concentrating, neck stiffness, sensitivity to light or sound, nausea, blurred vision, yawning and pallor. The terms *prodrome* and *warning symptoms* are best avoided because they are often mistakenly used to include aura.

The majority of migraine auras are associated with headache fulfilling criteria for 1.1 *Migraine without aura*. For this reason the entity 1.2.1 *Typical aura with migraine headache* has been singled out below. Migraine aura is sometimes associated with a headache that does not fulfil criteria for migraine without aura and, in other cases, migraine aura may occur without headache. These two subforms are also now distinguished.

Aura with similar features has also been described in association with other well-defined headache types, including cluster headache; the relationships between aura and headache are not fully understood.

Before or simultaneously with the onset of aura symptoms, regional cerebral blood flow is decreased in cortex corresponding to the clinically affected area and often including an even wider area. Blood flow reduction usually starts posteriorly and spreads anteriorly and is usually above the ischaemic threshold. After one to several hours, gradual transition into hyperaemia occurs in the same region. Cortical spreading depression of Leão has been implicated.

Systematic studies have demonstrated that many patients with visual auras occasionally have symptoms in the extremities. Conversely patients with symptoms in the extremities virtually always also suffer visual aura symptoms. A distinction between migraine with visual aura and hemiparaesthetic migraine is probably artificial and therefore is not recognised in this classification. Patients with motor weakness are classified separately because of the dominantly inherited form, 1.2.4 *Familial hemiplegic migraine*, and because of clinical differences. The genetic relationship between migraine with aura and familial hemiplegic migraine has not been established.

The previously-defined syndromes *migraine with prolonged aura* and *migraine with acute-onset aura* have been abandoned. The great majority of patients with such attacks have other attacks that fulfil criteria for one of the subforms of 1.2 *Migraine with aura* and should be coded to that diagnosis. The rest should be coded to 1.6.2 *Probable migraine with aura*, specifying the atypical feature (prolonged aura or acute-onset aura) in parenthesis.

1.2.1 Typical aura with migraine headache

Description:

Typical aura consisting of visual and/or sensory and/or speech symptoms. Gradual development, duration no longer than one hour, a mix of positive and negative features and complete reversibility characterise the aura which is associated with a headache fulfilling criteria for 1.1 *Migraine without aura*.

Diagnostic criteria:

- A. At least 2 attacks fulfilling criteria B–D
- B. Aura consisting of at least one of the following, but no motor weakness:
 - 1. fully reversible visual symptoms including positive features (*eg*, flickering lights, spots or lines) and/or negative features (*ie*, loss of vision)
 - 2. fully reversible sensory symptoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbness)
 - 3. fully reversible dysphasic speech disturbance
- C. At least two of the following:
 - 1. homonymous visual symptoms¹ and/or unilateral sensory symptoms
 - 2. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes
 - 3. each symptom lasts ≥ 5 and ≤ 60 minutes
- D. Headache fulfilling criteria B–D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
- E. Not attributed to another disorder²

Notes:

1. Additional loss or blurring of central vision may occur.
2. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but attacks do not occur for the first time in close temporal relation to the disorder.

Comments:

This is the most common migraine syndrome associated with aura. The diagnosis is usually evident after a careful history alone though there are rare secondary mimics including carotid dissection, arteriovenous malformation and seizure.

Visual aura is the most common type of aura, often presenting as a fortification spectrum, *ie*, a zigzag figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge leaving variable degrees of absolute or relative scotoma in its wake. In other cases, scotoma without positive phenomena may occur; this is often perceived as being of acute onset but, on scrutiny, usually enlarges gradually. Next in frequency are sensory disturbances in the form of pins and needles moving slowly from the point of origin and affecting a greater or smaller part of one side of the body and face. Numbness may occur in its wake, but numbness may also be the only symptom. Less frequent are speech disturbances, usually dysphasic but often hard to categorise. If the aura includes motor weakness, code as 1.2.4 *Familial hemiplegic migraine* or 1.2.5 *Sporadic hemiplegic migraine*.

Symptoms usually follow one another in succession beginning with visual, then sensory symptoms and dysphasia, but the reverse and other orders have been noted. Patients often find it hard to describe their symptoms in which case they should be instructed in how to time and record them. After such prospective observation the clinical picture often becomes clearer. Common mistakes are incorrect reports of lateralisation of headache, of sudden onset when it is gradual and of monocular visual disturbances when they are homonymous, as well as incorrect duration of aura and mistaking sensory loss for weakness. After an initial consultation, use of an aura diary may clarify the diagnosis.

Appendix B: Definition and background of chronic migraine(206):

Chronic migraine

Description:

Migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse.

Diagnostic criteria:

- A. Headache fulfilling criteria C and D for 1.1 *Migraine without aura* on ≥ 15 days/month for >3 months
- B. Not attributed to another disorder^{1;2}

Note:

- 1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12, or history and/or physical and/or neurological examinations do suggest such disorder but it is ruled out by appropriate investigations, or such disorder is present but headache does not occur for the first time in close temporal relation to the disorder.
- 2. When medication overuse is present and fulfils criterion B for any of the subforms of 8.2 *Medication-overuse headache*, it is uncertain whether this criterion B is fulfilled until 2 months after medication has been withdrawn without improvement (see *Comments*).

Comments:

Most cases of chronic migraine start as 1.1 *Migraine without aura*. Therefore, chronicity may be regarded as a complication of episodic migraine.

As chronicity develops, headache tends to lose its attack-wise (episodic) presentation although it has not been clearly demonstrated that this is always so.

When medication overuse is present (*ie*, fulfilling criterion B for any of the subforms of 8.2 *Medication-overuse headache*), this is the most likely cause of chronic symptoms. Therefore, the default rule is to code such patients according to the antecedent migraine subtype (usually 1.1 *Migraine without aura*) plus 1.6.5 *Probable chronic migraine* plus 8.2.8 *Probable medication-overuse headache*. When these criteria are still fulfilled 2 months after medication overuse has ceased, 1.5.1 *Chronic migraine* plus the antecedent migraine subtype should be diagnosed, and 8.2.8 *Probable medication-overuse headache* discarded. If at any time sooner they are no longer fulfilled, because improvement has occurred, code for 8.2 *Medication-overuse headache* plus the antecedent migraine subtype and discard 1.6.5 *Probable chronic migraine*.

These criteria require further study.

Appendix C: STROBE Statement—Checklist of items that should be included
in reports of *case-control studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
<i>Introduction</i> Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
<i>Introduction</i> Objectives	3	State specific objectives, including any pre specified hypotheses
<i>Methods</i> Study design	4	Present key elements of study design early in the paper
<i>Methods</i> Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
<i>Methods</i> Participants	6	(a) Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls (b) For matched studies, give matching criteria and the number of controls per case
<i>Methods</i> Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
<i>Methods</i> Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
<i>Methods</i> Bias	9	Describe any efforts to address potential sources of bias
<i>Methods</i> Study size	10	Explain how the study size was arrived at
<i>Methods</i> Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
<i>Methods</i> Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how matching of cases and controls was addressed (e) Describe any sensitivity analyses

<i>Results</i> Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
<i>Results</i> Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest
<i>Results</i> Outcome data	15 *	Report numbers of outcome events or summary measures
<i>Results</i> Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
<i>Results</i> Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<i>Discussion</i> Key results	18	Summarise key results with reference to study objectives
<i>Discussion</i> Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
<i>Discussion</i> Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
<i>Discussion</i> Generalisability	21	Discuss the generalisability (external validity) of the study results
<i>Other issues</i> Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix D: STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
<i>Introduction</i> Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported
<i>Introduction</i> Objectives	3	State specific objectives, including any pre specified hypotheses
<i>Methods</i> Study design	4	Present key elements of study design early in the paper
<i>Methods</i> Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
<i>Methods</i> Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants
<i>Methods</i> Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
<i>Methods</i> Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
<i>Methods</i> Bias	9	Describe any efforts to address potential sources of bias
<i>Methods</i> Study size	10	Explain how the study size was arrived at
<i>Methods</i> Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
<i>Methods</i> Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how matching of cases and controls was addressed (e) Describe any sensitivity analyses

<i>Results</i> Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
<i>Results</i> Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest
<i>Results</i> Outcome data	15 *	Report numbers of outcome events or summary measures
<i>Results</i> Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
<i>Results</i> Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
<i>Discussion</i> Key results	18	Summarise key results with reference to study objectives
<i>Discussion</i> Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
<i>Discussion</i> Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
<i>Discussion</i> Generalisability	21	Discuss the generalisability (external validity) of the study results
<i>Other issues</i> Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix E: Publications throughout the course of the MPhil

Oral Presentation:

Ray S, Singh S, Curran A, Halford J, Harrold J, Kumar R. Design and inception of a study to explore putative links between migraine, appetite behaviours and obesity in children. Department of Neurology, Alder Hey Children's NHS Foundation Trust, Liverpool; Institute of Child Health, University of Liverpool, Liverpool, UK; Department of Psychology, University of Liverpool Liverpool, UK. *Royal College of Paediatrics and Child Health Annual Conference, Warwick, April, 2010.*

Poster Presentation:

Ray S, Kumar R. Paediatric headache: referral patterns and management within an outpatient tertiary paediatric neurology clinic. European Paediatric Neurology Society Congress, Harrogate. September 30th 2009.

Paper publication:

Ray S, Kumar R. Migraine and Obesity. Cause or effect? Headache. 2010 February;50(2):326-328.

Kumar R, Ray S. Safety considerations in prescribing topiramate in adolescents. Pediatrics. 2009 June 10th. E-letter.

Appendix F: Letter to the editor:

This is the pre-peer reviewed version of the following article [Ray ST, Kumar R. Migraine and obesity: cause or effect? Headache. Feb;50(2):326-8](231), which has been published in final form at [http://onlinelibrary.wiley.com/doi/10.1111/j.1526-4610.2009.01539.x/abstract].

The letter below was written in response to the study by Hershey et al(107). It was accepted by the International Journal Headache – the Journal of head and face pain.

Title: Migraine and obesity: cause or effect?

Authors: Stephen TJ Ray, Ram Kumar(MSc) (Ray S, Kumar R).

Affiliations: Alder Hey Children’s NHS foundation trust, Liverpool, England.

Conflict of interest: No Conflict.

Key words: Migraine, Obesity, BMI, appetite, eating behavior, adiposity.

Letter to the editor:

Abbreviations: **BMI** – Body mass index, **pedMIDAS** – pediatric migraine disability assessment, **FTO** - The fat mass and obesity associated **CSF** - cerebrospinal fluid.

Migraine and obesity: cause or effect?

We read with interest the paper by Hershey et al (1) showing that obesity was significantly correlated with headache frequency and disability in children as has been observed in adult population studies. We wish to highlight certain aspects of their method for further consideration. The study was a large, multi-centre, retrospective case – only series. Previous studies in this area have used categorical variables when measuring weight and migraine severity. This study used the PedMIDAS scale to measure headache severity, and measured adiposity with BMI centiles. This methodology is an advance

in the area since by utilising effectively continuous measures there is a higher power to detect an association. Raw BMI, as used in the study of Hershey et al, has been considered a poor measure of adiposity in the normal weight range in children because it does not distinguish well between fat and lean mass⁽ⁱⁱ⁾. By contrast, the use of BMI Z scores have been described as optimal for assessing adiposity on a single occasion⁽ⁱⁱⁱ⁾.

The authors detected a statistically significant association between BMI percentile and measures of headache severity. The association was modest ($r = 0.10$ and 0.08 for headache frequency and pedMIDAS respectively). One reason for this could be the incorporation of all primary headache types into the study. Previous associations between headache and obesity have been detected specifically within the category of migraine rather than tension-type headache^(iv). It has been shown that obesity is a risk factor chronic migraine rather than chronic tension-type headache^(v), and that high BMI increases migraine frequency^(vi). It would thus be interesting to perform a sub analysis in the group of patients having migraine with and without aura. Another reason for the low correlation between BMI and the measures of headache severity could be that there may be a non-linear association.

Pinhas-Hamiel et al^(vii) reported findings in line with the current study of Hershey et al. The study found that overweight females had a four times greater risk of headache compared to normal weight females (OR=3.93). The methodology of this study was a case control of 273 children.

The authors note that the overall obesity prevalence in the cases reflected the latest general U.S paediatric obesity rates. The authors suggest that this may be due to some overweight children developing headaches that require treatment later in life; accounting for the increased representation of migraine among obese individuals in the adult population. This ties in with the hypothesis by Bigal and Lipton, that obesity is a risk factor for migraine chronification^(viii).

Alternatively, we hypothesize that migraine in children may increase adiposity, via eating behaviours. This is a biologically plausible hypothesis.

Firstly, because of the overlapping neurobiological mediators in migraine, appetite and obesity. For example, Calcitonin Gene Related Peptide (CGRP), is raised in the plasma of obese adults; it is also raised in the external jugular venous blood of animal models of obesity and also migraine patients. ^(ix,x,xi). In the rat model of obesity, administering exogenous CGRP increases intake of fat, and CGRP is elevated prior to the onset of obesity in animal models. CGRP and its receptors are now a major focus for pharmacological treatment of migraine ^(xii,xiii). Serotonin is another neurotransmitter pertinent to obesity, migraine and appetite. In appetite, serotonin is key to the process of feeding control including satiation, and signaling the satiety state. Serotonin agonist drugs given to humans markedly reduce their appetite ^(xiv,xv), leading to weight loss ^(xvi). Migraine, on the other hand, has been characterised as a condition of relative brain serotonin deficiency. Thus one could hypothesize that in migraineurs there is a tendency for increased appetite ^(xvii). There is increasing interest in the role of orexins, in particular orexin A, in appetite control. Orexins are also involved in migraine. Orexin A levels were elevated in the cerebrospinal fluid (CSF) of migraine patients ^(xviii). It has been argued this is a compensatory response to chronic pain, for it has been suggested orexin A has antinociceptive properties ^(xix). Orexins are incontrovertibly involved in the regulation of appetite behaviour ^(xx). Administration of orexin A to rats increases appetite and delays satiety^(xxi), and orexin -1-receptor antagonists reduce appetite substantially in rats^(xxii). This overlap shows a crucial neurobiological link between eating behaviour and migraine, and underlines the importance of studying appetite and resulting eating behaviours, rather than just established obesity in this paradigm.

Furthermore, there is interest in appetite behaviours as a mechanism for the development of obesity in children. Recent evidence suggests that neurobiological mediators of interindividual susceptibility to obesity can act via eating behaviour ^(xxiii,xxiv,xxv,xxvi). Willer et al reported that the common genes involved in human obesity are expressed in the central nervous system, implying the importance of studying behaviours to understand the control of weight ^(xxvi). The fat mass and obesity associated (FTO) gene, expressed in the hypothalamus, has received much recent interest since a common single nucleotide polymorphism was associated with obesity and

increased adiposity in children. Wardle et al have demonstrated the effect of the FTO genotype on increased adiposity being mediated through patterns of eating behaviour^(xxiii). Another recent study in children from an ingestive laboratory demonstrated that the FTO polymorphism alters food choice towards energy-dense foods, independent of the child's current weight category ^(xxvii). Thus poor eating behaviours could increase adiposity, i.e. children who are currently within the "normal" weight range, but at risk of proceeding to overweight and obese categories ^(xxviii). Findings that a neurobiological factor(the FTO gene) cause increased adiposity via its effects on appetite and eating behaviour, highlight that it is plausible that other neurobiological causes, such as migraine, could act similarly to have the same effect on adiposity.

We feel it will be necessary to study the effects of migraine on eating behaviour. If a relationship exists between migraine and increased appetite, it may be possible to modify treatment before the establishment of obesity. Interventions to modify appetitive traits or ameliorate their impact on weight can be designed ^(xxix). Studying this in the paediatric population will further our understanding of the relationship between migraine and adiposity. Since both migraine and obesity evolve during the course of childhood, a study in the childhood population may be able to establish if migraine precedes the onset of obesity or vice versa, thus determining the causality of this relationship. We feel a prospective study confined to migraine patients will enhance results of the study by Hershey et al.

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Appendix G: Patient information sheet:



A study on the link between migraine, appetite behaviours and obesity.

We would like to invite you and your child to participate in our research study. Before you decide to participate, we shall explain below why we are doing this study, and what it will involve for you and your child.

Please take time to read the following information and discuss it with others if you wish. You can ask us for further information (see contact details at the end of this sheet).

Why are we doing this study?

Migraine can be a very disabling disease, and it is very common in children. There has recently been research in adults to suggest there is a link between severe migraine and obesity, which can cause worse headaches. Obesity is becoming very common in children, with 25% of children classified as obese. We therefore think it is important to investigate if severe migraine can cause poor eating in children leading to obesity. We aim to see if particular appetite behaviours can be seen in migraine patients, so that they can be addressed, and doctors can devise ways in which to change them to prevent the onset of obesity and worsening the patients' migraine.

Why have you and your child been chosen?

Based on the records at Royal Liverpool Children's Hospital, your child was noted to either have suspected migraine or have been diagnosed with migraine. You may remember meeting the leader of this study (Dr Ram Kumar) at a previous clinic appointment for your child's headache. We would like some information on how your child is doing from a health and education point-of-view.

Do I have to take part?

It is up to you whether you take part in this research study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect any future medical care.

What do my child and I have to do if we take part?

We would like to invite you to attend the neurology department for a clinic appointment with the researchers. Whilst your child is attending for their appointment with the consultant, either prior to or after the appointment, the researcher will take you into a separate room, where firstly he will explain what the research is about and why we would like your child to be involved. Then we will explain the types of questions we are going to ask you and your child. Then we will ask you if you have any questions. Then we would ask whether you would like to take part. If you agree to do so, we will ask you, and your child to sign a consent form. Then we will ask you and your child all the questions from the questionnaires. This will take no more than one hour to complete. This is all we need you to do, once the study is finished, if you should wish, we will send you results of the study.

What are the possible benefits of taking part?

You and your child will be contributing to improving the care and health of other children in the future who are also diagnosed with migraine.

What are the possible disadvantages and risks of taking part?

We do not foresee any disadvantage to you or your child if you decide to take part in the study. There are no risks involved to you or your child, and no pain or discomfort will be caused. If you or your child become upset by any of the issues that arise from the questionnaires the consultant will happily give you counselling about them. Furthermore, if you have any concerns about the way in which you were approached or treated throughout the course of the research you can contact the hospital research department to voice your concerns (Details below).

Will my taking part in this study be kept confidential?

We will keep all records from your child’s questionnaire confidential. Only the named members (at the end of this sheet) of the research study team will have access to the records.

What will happen to the results of the research study?

We will analyse the results from all the participants in this study at the end of the study period. We will publish a report on our conclusions in a well-reviewed medical journal. In addition, we will send you a copy of the report if you would like one.

Who is organising and funding the research?

This research study has been organised by the paediatric neurology department, Royal Liverpool Children’s NHS Foundation Trust. There is no external funding for this study; the primary researcher has been funded to conduct the study by the Neurodisability trust.

Who has reviewed the study?

The Cheshire Research Ethics Committee has reviewed this study.

Contact for further Information

Please contact the research study members if you need any further information at any stage:

Dr Ram Kumar Consultant Paediatric Neurology, Department of Paediatric Neurology, Royal Liverpool Children’s Hospital, Eaton Road 01512525164	Stephen Ray Mphil Researcher Department of Paediatric Neurology, Royal Liverpool Children’s Hospital, Eaton Road 07709453694	Dot Lambert Research and Development Manager Alder Hey Children's NHS Foundation Trust Direct tel: 0151 252 5673 Internal ext: 3785
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