A Cross-sectional Paediatric Pilot Study of Migraine, Eating Behaviours and Adiposity

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master in Philosophy by Shashi Singh

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Contents

Abstract

Objective

The primary aim was to compare eating behaviours between migraine cases and non-migraine headache controls. The secondary aim was to assess the relationship migraine severity and monthly headache frequency share with eating behaviours, food intake, food cravings and adiposity among migraine cases.

Background

Recent research has highlighted an association between migraine and adiposity, in adults and children[39-41,46-50]. However the direction of causality between migraine and adiposity has not yet been established. There are overlapping neurobiological mechanisms in migraine, eating behaviours and adiposity[116-125]. Migraine has been noted to affect appetite[1,146], but this has not been formally studied. This pilot study explored the biologically plausible hypothesis that migraine may lead to obesity, via alterations in appetite, food intake and food cravings.

Methods

A single-centre, cross-sectional, questionnaire-based, clinical migraine population pilot study was designed. The two migraine measures were migraine severity as measured by the PedMIDAS tool and monthly headache frequency. Eating behaviours were assessed using the Dutch Eating Behaviour Questionnaire (DEBQ) and Child Eating Behaviour Questionnaire (CEBQ). Food cravings were measured by the Food Craving Inventory (FCI-II) and food intake was assessed using the Food Intake Questionnaire (FIQ). Adiposity was indirectly measured using BMI z-scores. Local Research Ethics and Trust R&D approvals were granted in June 2009.

Results

Sixty children aged 5-17 years were recruited from neurology/general paediatric clinics. Insufficient control patients were recruited (n=7). The desire to drink subscale of the CEBQ had a significant positive correlation with the PedMIDAS scores (r_s= 0.41, p= 0.01). Monthly headache frequency had a significant positive correlation with the negative marker food scores of the FIQ (r_s= 0.27, p= 0.04).

Conclusion

The primary objective to compare eating behaviours between migraine cases and non-migraine headache controls was not achieved. Migraine severity (as measured by the PedMIDAS scores) is weakly associated with the desire to drink (as measured by the CEBQ). Monthly headache frequency is weakly associated with the intake of unhealthy foods eaten the day before. It must be noted there is only weak evidence for the conclusions given the small sample size of this pilot study.

Background

Body mass index as a proxy for adiposity is positively correlated with migraine severity, headache frequency and migraine prevalence[39-41,46-50]. Restrained, emotional, externalised and hedonistic driven eating behaviours are strongly associated with increased adiposity levels[71-81]. Migraine, appetite and adiposity share an overlap in neurobiological mechanisms that include alterations of serotonin, calcitonin gene related peptide (CGRP), orexin A, leptin and hypothalamic pathology[116-125]. Migraine patients can develop food cravings during the prodromal and ictal phase of acute attacks[1,46]. Preventive migraine treatments such as topiramate and pizotifen can affect appetite levels that lead to adverse weight altering effects[151-154].

Based on the information presented so far it is possible that there is a causal relationship between migraine, eating behaviours and adiposity. However no study hitherto has investigated the relationship of all three variables together. Hence this pilot study was developed to investigate the relationship that migraine shares with eating behaviours and adiposity. This pilot study was also used to identify limitations in the methodology to help prepare for a larger future study on “migraine, eating behaviours and adiposity”. This main future study will be designed to confirm and extend the findings from this present pilot study. Power sample size calculations for the main future study have been presented in this thesis.

Chapter 1: Introduction

Chapter 1.1

Migraines

Migraine definition

Migraine is a clinical syndrome that may consist of a headache component with specific features and associated symptoms[1]. The headache phase can typically last 4 to 72 hours, which is characteristically a unilateral, pulsatile and intermittent moderate to severe pain. In children this headache phase is usually short lived, lasting between 2 to 48 hours[2]. Migraine is commonly associated with symptoms of nausea, vomiting, photophobia and phonophobia[3]. Usually, a minimum of five acute headache attacks with migraine features suggest a diagnosis of migraine without aura. Secondary headaches resulting from infection and other causes must be excluded prior to making any migraine diagnoses[4]. The most common differential diagnosis for migraine is tension type headache (TTH), which is typically a bilateral, pressing or tightening band of pain around the head. The pain is usually of mild to moderate intensity, which can be unresponsive to analgesic medications and does not worsen with routine physical activity[1].

A migraine aura is any reversible focal neurological symptom that usually develops over 5 to 20 minutes and can last up to a hour[1]. The aura may manifest as visual disturbances (e.g. visual perception of flickering lights, spots, lines or loss of vision), sensory symptoms (e.g. numbness and paraesthesia) or motor weakness[5]. An aura can be diagnosed when alternative causes for the focal neurological symptoms (e.g. transient ischaemic attack) have been excluded. Migraine headaches with aura are less common than migraine headaches without aura[6].

Migraine prevalence

Migraines and other primary headache disorders can account for up to 27% of all paediatric neurology referrals (based on an unpublished audit at Alder Hey Children's Hospital, Liverpool). As outlined in table 1.1.0, migraine prevalence in the UK varies according to age. It ranges from 1.2-3.2% in children aged between 3 and 7 years (male predominant prevalence) to 28% in adolescents aged between 15 and 19 years (female predominant prevalence)[7,8].

Age	UK migraine prevalence (%)
3 to 7 years	1.2- 3.2
7 to 11 years	4- 11
11 to 15 years	18- 23
15 to 19 years	28

Table 1.1.0- Migraine prevalence according to age (listed as percentage figures)

Migraines are ubiquitous to almost every nation and ethnic race, which can have a serious impact on employment, social activities and domestic function[9]. There is an impaired quality of life with substantial socioeconomic burdens attributable to increased medical needs, reduced employment efficacy and work absences[10]. The World Health Organisation (WHO) has ranked migraines as the 19th most debilitating medical condition worldwide[11]. Over a period of 2 weeks, greater than 900, 000 children with migraine miss 164,454 days off school[12].

Migraine pathophysiology

The current understanding of migraine pathogenesis is still incomplete[13]. Various mechanisms have been proposed in migraine pathology however the exact sequence in which these mechanisms occur has not been established[14]. The current concepts of these mechanisms are now discussed.

Cortical spreading depression (CSD)

Cortical spreading depression (CSD) is a self-propagating wave of spontaneous depolarisation of neuronal glial cells[15]. It initially affects neurons located in the occipital cerebral cortex but then spreads through adjacent cells towards the frontal cortex in a marching sequence[16]. There is associated release of potassium, nitric oxide and proteases that alter the permeability of the blood brain barrier. Consequently cell perfusion is affected which causes cerebral blood flow changes during acute migraine attacks[17]. Cortical spreading depression is the key mechanism thought to trigger the onset of aura symptoms[18].

Trigeminal Pathway

The trigeminal pathway is formed by a circuit of afferent nerves that densely innervate the brain meninges and propagate nociceptive impulses to the sensory cortex for pain processing[19]. During acute migraine attacks there is stimulation of trigeminal afferent fibres located along the extra-cranial vessels that transmit nociceptive impulses along the trigeminal pathway[20]. There is subsequent cortical processing, which results in the perception of a pain sensation during an acute migraine attack[21]. Trigeminal nerve activation precipitates the release of various neuro-chemicals such as calcitonin gene related peptide (CGRP) which potentiates the pain response and causes vasodilatation in cerebral blood vessels[22]. The importance of CGRP in migraine pathology is discussed later in chapter 1.4. The putative trigeminal pain pathway is accepted as an integral process to migraine pathology however the trigger mechanism behind its activation is still unknown[23].

Neurogenic inflammation

Upon trigeminal nerve activation, the release of bioregulatory peptides such as CGRP and glutamate induce a state of "sterile neurogenic inflammation", within the blood vessel walls of the meninges. This is characterized by oedema formation (plasma extravasation), vasodilation and the release of pro-inflammatory mediators such as bradykinin[22]. This inflammatory process has been inhibited by clinically effective anti-migraine agents such as ergotamine[19]. Neurogenic inflammation may promote stronger and more frequent trigeminal pain trafficking which leads to the further release of pro-inflammatory substances[24].

Central sensitisation

Sensitization occurs when the stimulus needed to generate a nerve response decreases over time, while the amplitude of the response to any given stimulus increases[25]. Central sensitisation of the trigeminal nucleus caudalis has been demonstrated during a migraine attack. In migraine patients there is a mal-adaptation of pain perception which can result in allodynia (the perception of pain to a non-painful stimulus) and hyper-algesia (intensified pain in response to a stimulus that ordinarily causes mild pain)[26]. Even after the headache phase of migraine has subsided, allodynia and hyperalgesia can persist for a long period of time, which may account for the long duration of some severe migraine attacks[27].

Migraine management

Conservative management of migraine involves identifying and then avoiding the exacerbating or trigger factors for acute attacks. These include avoiding stress, keeping good sleep hygiene (i.e. regular bedtimes), routine exercise, food diaries to identify potential

dietary triggers, staying well hydrated and a balanced diet with regular meal times[28]. These strategies are reported to reduce the pain burden of migraine[29].

Acute pharmacological therapies for migraine are broadly divided into 2 categories of non-specific treatments and specific treatments[1]. Non-specific treatments such as paracetamol (acetaminophen), non-steroidal anti-inflammatory drugs (NSAID's) and opioids are appropriate for the treatment of mild to moderate migraine attacks. Specific treatments include ergotamine and triptan agents (e.g. zolmitriptan and sumatriptan), which are usually first line drug treatments for moderate to severe migraine attacks[30].

Preventive therapy is reserved for severe migraine cases. The main goal is to reduce the frequency and intensity of migraine attacks thereby improving patient functioning and quality of life[31]. Pizotifen is a serotonin antagonist routinely used as a first line preventive medication for migraine patients aged over 2 years[32]. Beta blockers such as timolol and propranolol are first line agents for migraine prophylaxis, but are contraindicated in asthma patients[33]. Topiramate, originally an anticonvulsant now used as an anti-migraine agent, is shown to more than halve monthly headache frequency[34]. The proposed pharmacology of topiramate ranges from the blockade of voltage-sensitive sodium channels to enhancing GABA-evoked chloride currents[35].

Migraine co-morbidities

Migraine patients are at three times greater risk of developing depression and generalised anxiety compared with non-headache controls[36]. Sleep disturbances, bruxism (clenching of the jaw and teeth grinding), co-sleeping with parents and snoring are associated with migraines in children[37]. Binge eating disorders have been associated with migraine in the female population, which has been hypothesised to be based on a common neuro-chemical overlap in serotonin dysfunction[38]. Adiposity as measured by body mass index has been correlated with migraine severity and headache frequency[39,40,41].

Chapter 1.1.1

Migraine and Adiposity

This pilot study was particularly interested in the relationship between migraine and adiposity[39-41]. Previous studies on migraine, headaches and adiposity have been reviewed in this chapter (see tables, 1.1.1 to 1.1.7) using a simplified criterion (see table 1.1.0a) which was adapted from the STROBE criteria and checklist[42] (STrengthening the Reporting of OBservational studies in Epidemiology). The STROBE tool is a validated criterion for reviewing observational studies[43]. See appendix 5.1.1a for the search methods used to identify the studies that have been reviewed and appendix 5.1.1b for an outline of the original STROBE criteria.

Criteria	Item No.	Recommendation
Title	1	Indicate the study's design with a commonly used term in the title or the abstract.
Objective	2	State specific objectives, including any pre-specified hypotheses.
Study Design	3	Present key elements of study design early in the paper.
Participants & settings	4	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.
Variables	5	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.
Main results	6	An outline of the main study findings.
Bias & limitations	7	Describe any potential sources of bias and outline the study limitations.

Table 1.1.0a- Adapted STROBE criteria used to used to review the headache and adiposity studies.

Author	Scher et al (2003)[39]
Title	Factors associated with the onset and remission of chronic daily headache (CDH) in a population-based study. It must be noted that Scher et al[39] defined CDH cases as patients that suffered from 180 annual headaches or more.
Objectives	This study aimed to identify risk factors for chronic daily headache (CDH) prevalence, incidence and remission in a US adult population.
Study Design	Prospective cohort study
Participants	A total of 55, 255 potential cases and controls were telephone interviewed at baseline. A total of 1,932 participants were telephone interviewed at 11 months follow-up. Patients were aged 18-65 years.
Variables	Annual headache frequency, duration of headaches and speed of headache were reviewed at both telephone interviews to assess for progression or remission of headaches. Patients were categorised as either CDH cases (180+ annual headaches) or controls (2-104 annual headaches). Body mass index was calculated as; [weight (pounds)/ height (inches)^2] x 703). Height and weight measurements were self reported over telephone interviews. Patients were also categorised as normal weight (BMI<25), overweight (BMI≥25) or obese (BMI≥ 30).
Data source/Measurement	All information for each variable was ascertained through the telephone interviews. Hence there was a high possibility of under-reported weight and BMI and over-reported height as they were not objectively measured by a researcher, but instead were self reported[44].
Study size	No description is given of how the study sample size was calculated.
Descriptive data	28% of controls and 20% of cases were male. 71% of controls and 80% of cases were cases. The mean age was 40 years for cases and 41 years for controls.
Main results	Chronic daily headache was significantly associated with obesity (odds ratio= 5.53).
Bias and limitations	The time elapsed from baseline to follow up was 2 months longer for controls than cases because the study quota for controls was filled more quickly than cases. This meant that control patients had a longer time period for any changes in headache features/characteristics to occur by the time of follow-up. At baseline headache frequency was evaluated by the number of headaches per year, whilst at follow up headache frequency was determined by the number of headache days per year. Hence headache frequency may have been under reported at follow up. Headache diagnoses were not stated and hence the application of results to sub populations of specific headache disorders such as migraine is not possible.
Other comments	The large sample size indicates there was a high power in which to detect true positive significant results. As patients were prospectively followed up this is one of few studies to investigate adiposity as a risk factor for headaches.

Table 1.1.1- Review of the Sher et al (2003)[39] study using an adaptation of the STROBE review[42]

Author	Bigal et al (2005)[40]
Title	Obesity and migraine: A population study
Objectives	The objective was to investigate the association BMI has with migraine prevalence, headache frequency/pain severity and associated migraine symptoms.
Study Design	Although clearly a cross sectional study, not once was the exact study design mentioned in the methods.
Settings	Households in 3 large metropolitan US areas were selected for telephone interview using random digit dialling methods (not otherwise specified in study article).
Participants	3, 791 migraine patients aged 18 to 89 years
Variables	Body mass index (BMI), migraine prevalence, headache frequency, headache duration, headache related disability, presence of photophobia/phonophobia, nausea/vomiting.
Data source/Measurement	BMI was calculated as following; [weight (pounds)/ height (inches)^2]x 703. Height and weight measurements were self reported in telephone interviews. Subjects were grouped according to BMI; underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), obese (30-34.9) and morbidly obese (≥35). The second edition of the International Classification of Headache Disorders (ICHD-II)[1] was used as a guide to making migraine diagnoses. Headache disability was assessed using a 10-point likert scale (0= no disability and 10= severely disabling). Chronic daily headache patients defined as greater than 15 headache days a month were excluded from data analysis.
Main results	BMI and the frequency of migraine attacks were associated. Obese individuals were three times more likely to suffer from 10-15 headache days a month than normal weight patients. The proportion of subjects with severe migraine pain increased with BMI, which was twice as high in the morbidly obese compared to the normal weight adults. Obesity was associated with more frequent headache related one day absences from school and work. Headache features such as photophobia and phonophobia were also more prevalent in obese individuals. Exacerbation of headaches from physical activity was twice as common in morbidly obese patients compared with versus normal weight individuals.
Bias and Limitations	This study used telephone interviews to obtain self reported height and weight measurements. This method was prone to under reporting of BMI and weight, as well as over reporting of height. There was no strict inclusion criteria applied to the recruitment process. This study did however comment on potential confounding factors such as food triggers, exercise and depression, that were not controlled in the study. Using the ICHD as a foundation for making headache diagnoses may have increased the accuracy of identifying true positive migraine patients but diagnoses were still self-reported.
Interpretations and generalisability	The large sample of patients used indicates there was a high power to detect true positive significant results. Females were over represented due to interviews conducted during business working hours. Data was however stratified for sex, age, educational background and ethnicity.

Table 1.1.2- Review of the Bigal et al (2005)[40] study using an adaptation of the STROBE review[42]

Author	Bigal et al (2006)[41]
Title	Obesity is a risk factor for transformed migraine but not chronic tension-type headache.
Background	In order to understand the Bigal et al (2006)[41] study a background to the diagnoses of transformed migraine (TM) and chronic tension type headache (CTTH) must be given. Transformed migraine is defined as 15 or more monthly headaches (that each last a minimum of 4hours) with at least 12 migraine attacks in the prior year (Silberstein and Lipton criteria[45]). Chronic tension type headache is defined according to the ICHD-II as 15 or more tension type headaches a month[1].
Objective	To investigate the relationship chronic migraine and chronic tension type headache have obesity.
Study Design	Cross-sectional study
Participants	There were 1,264 chronic daily headache (CDH) cases (≥15 monthly headaches lasting a minimum of 4 hours) and 25, 585 controls (<15 monthly headaches), aged 18 to 89 years. CDH patients were further divided into two groups of TM patients (n= 401) and CTTH patients (n= 863).
Variables	Headache induced disability was assessed by the number days absent from school or work in the past 3 months. Based on a pain scale numbered 1 to 10, headaches were categorised as mild (1 to 3), moderate (4 to 7) or severe (8 to 10). Headache frequency, duration and associated symptoms were also assessed. All headache outcome measures were assessed as a function of BMI. BMI was calculated as ([weight (pounds)/ height (inches)^2]x703). Height and weight measurements were self reported over telephone interviews. Subjects were grouped according to BMI; underweight (<18.5), normal weight (18.5-24.9), overweight (25-29.9), obese (30-34.9) and morbidly obese (≥35).
Main results	Chronic daily headache prevalence was significantly higher in the obese and severely obese groups. BMI was positively correlated with transformed migraine prevalence (TM was twice more likely to occur in morbidly obese patients compared with normal weight individuals). BMI greater than 25 was associated with a higher proportion of headache associated disability The proportion of patients reporting 50% of their headache attacks resulting in severe pain was higher among all individuals with a BMI> 25. Morbidly obese patients were at 1.9 times greater risk of suffering from severe headache attacks compared with normal weight individuals.
Bias and limitations	This study has analysed data derived from the same patient sample that was telephone interviewed in the Bigal et al (2005)[40] study. Based on the methodology details it appears that this study (Bigal- 2006[41]) use the same sample of patients but differ in the information extrapolated from the available data. At no point is this explicitly stated in either of the two studies. Based on the methodology of data collection and patient sample the limitations for this study are the same as for the Bigal et al (2005)[40] study. Headache diagnoses were self-reported by patients and not based on a clinical diagnosis from a physician. Potential confounders such as exercise and food triggers were not measured in this study. Headache induced disability was assessed by the number work/school day absences in the last 3 months. However this method would have been invalid for unemployed adults.

Table 1.1.3- Review of the Bigal et al (2006)[41] study using an adaptation of the STROBE review[42]

Author	Pinhas-Hamiel et al (2008)[46]
Title	Headaches in overweight children and adolescents referred to a tertiary care centre in Israel.
Objective	This study aimed to assess the association between obesity and primary headaches in children and adolescents.
Study Design	Pinhas-Hamiel et al (2008)[46] described the study as a cross-sectional study, when in fact the methodology was of a case-control study.
Settings	Obese children were recruited from a hospital obesity clinic and non-obese children (controls) were recruited from community general paediatric clinics.
Participants	273 children aged 9 to 17 years old.
Variables	Participants were assessed for the presence of any headache disorders using a short questionnaire adapted from the International Headache Society (IHS) diagnostic criteria. Monthly headache frequency, duration of headache attacks, character of pain (location, pulsation & severity) and the presence of any associated symptoms such as nausea, vomiting and photophobia. Height and weight measurements were obtained from the national Israeli database (however this point is not clearly stated in the study). Body mass index was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Specific details about how height and weight measurements were taken were not outlined in the study. Patients were categorised according to the following groups: Overweight (BMI> 95^{th} percentile), at risk of being overweight (BMI between 85^{th} to 95^{th} percentile) or normal weight (BMI< 85^{th} percentile).
Main results	The proportion of subjects with headaches in the overweight group was 17.9% versus 10.3% in the normal weight group. Children with headaches were significantly heavier (p=0.03) than headache free subjects. Headaches were present in 17.9% of the “overweight” children, in 15.6% of the “at risk of being overweight” children and in 10.3% of the “normal weight” children. After adjusting for age and blood pressure, overweight girls were four times more likely to suffer headaches than normal weight girls.
Bias and limitations	Children with eating disorders were excluded from the study indicating that some potential confounding factors were acknowledged, however food triggers and depression were unaccounted for in the study. Children recruited from obesity clinics may have received weight altering treatment in the form of exercise prescription, medication or dietary intervention. Such factors may have biased results considering their relationship to both adiposity (as measured by BMI) and headaches. It is not clearly stated whether height and weight were measured at clinic visits or obtained from a national database as implied by the wording used in the article.

Table 1.1.4- Review of the Pinhas-Hamiel et al (2008)[46] study using an adaptation of the STROBE review[42]

Author	Hershey et al (2009)[47]
Title	Obesity in the paediatric headache population: A multicenter study
Objective	The aims of this study were to examine the relationship between weight and headache frequency/disability, and also assess the effect of weight change on headache outcomes within a paediatric headache population.
Study Design	Retrospective audit
Participants and setting	913 children aged 3 to 18 years were recruited from headache specialty clinics located in 5 hospitals, 2 private practice groups and the American headache society.
Variables	Height and weight measurements were taken at clinic visits, which were later converted to BMI percentiles. Further details of how height and weight measurements were taken were not outlined in the study. Overweight was defined as a BMI over the 85th percentile. Disability from headaches was measured using the PedMIDAS questionnaire. This tool measured the total number of days absent from social, domestic, school and sporting activities in the last 3 months. Monthly Headache frequency was also noted in the initial clinic visit. As part of routine care, dietary advice was provided to all patients at the initial clinic visit. The correlates for BMI percentile, disability and frequency of migraine attacks were analysed at baseline and then at 3 months and 6 months follow up.
Main results	There was a very weak positive correlation between headache frequency and BMI (r= 0.1, p=0.003). Headache related disability was associated with BMI percentiles. At 3 months follow up weight loss in the overweight group was observed in association with decrements in headache frequency ($p \leq 0.01$). At 6 months follow-up, BMI reduction in overweight children was associated with a reduction in the frequency of headache attacks ($p \leq 0.01$). Weight loss in the overweight children at both 3 and 6 months follow-up was associated with reduced monthly headache frequency.
Bias and limitations	Some patients were given preventative medications such as topiramate which can induce weight loss[48], and hence may have biased results. At 3 months post baseline 700 patients (76.7%) were not followed up, the reasons for which were unexplained. At 6 months another 39 patients were not followed up. The discrepancy in sample sizes from 913 patients at baseline to 213 patients at 3 months and then 174 patients at 6 months suggest that any change witnessed at follow up will have been amplified due to the considerably smaller sample sizes. The fact that the clinics offered dietary advice at the initial visit may have provoked to some extent the weight loss documented. Considering some form of dietary intervention was put in place, there was no measure of whether eating played any part in the results produced. A change in appetite may have masked the relationship between BMI and headaches, specifically that of migraine.

Table 1.1.5- Review of the Hershey et al (2009)[47] study using an adaptation of the STROBE review[42]

Author	Kinik et al (2009)[49]
Title	Obesity and paediatric migraine
Objective	This study aimed to assess the impact of obesity on the severity and frequency of migraine attacks.
Study Design	Retrospective case series
Participants and settings	Medical records were reviewed for 124 children aged 4 to 17 years who previously attended a Turkish Neurology clinic, from March 2000 to September 2006.
Variables	Patient files were reviewed for information on the frequency, duration and severity of migraine (headache) attacks, as well as the presence of any associated symptoms (aura, nausea, vomiting, photophobia and phonophobia). 124 patients that fulfilled the criteria for a migraine diagnosis according to the ICHD-II[1] were included in the final analysis (see appendix 5.1.9 for details on the ICHD-II criteria for migraine diagnosis). Data on migraine severity as quantified by a 10 point visual analogue scale (mild/moderate headaches= 1 to 7 points; severe headaches= 8 to 10 points) and monthly attack frequency were ascertained from the case files. Body mass index (BMI) values previously calculated as weight in kilograms divided by height in metres squared (kg/m^2) were also extracted from case notes. Further details of how height and weight measurements were taken were not outlined in the study. Relative BMI (relBMI) values were then calculated using the formula; (raw BMI value x100)/ (50^{th} percentile of BMI value adjusted for age and sex). Patients were categorised according to three adiposity groups; normal weight (relBMI <110), overweight (110≤relBMI≤120) and obese (relBMI>120).
Main results	Results showed that obese children suffered more frequent migraine attacks compared with normal weight and overweight subjects (p= 0.02). Relative BMI had a very weak positive correlation with headache frequency (r= 0.2, p= 0.03). Migraine severity and associated symptoms did not share any significant relationship with relative BMI.
Bias and limitations	Given that some anti-migraine medications can alter weight[48] this study eliminated one confounding factor by excluded patients on any form of medication. The migraine diagnoses were made by specialist neurologists in accordance with the validated IHS criteria[1]. This indicates a high probability that the migraine diagnoses were clinically valid. Given that migraine severity was not assessed through use of a validated tool, it may not have been accurately measured and would account for the insignificant correlations between migraine severity and BMI. Study limitations and potential biases were not outlined in this study.

Table 1.1.6- Review of the Kinik et al (2009)[49] study using an adaptation of the STROBE review[42]

Author	Nelson et al (2010)[50]
Title	Headache and Biomarkers Predictive of Vascular Disease in a Representative Sample of US Children
Objective	The aim of this study was to examine the association of childhood headache disorders with markers of risk for cardiovascular and cerebrovascular disease, such as obesity.
Study Design	Cross-sectional study
Participants and settings	Data previously collected from the National Health Examination and Nutrition Survey (NHANES) from 1999 through to 2004, was analysed. Information was provided on 11,770 U.S resident children aged 4 to 19 years. Patients included in the review had their headache status previously determined by asking the following closed question; "in the last 12 months have you had frequent or severe headaches including migraine?" Records on body mass index (BMI) calculated as weight in kilograms divided by height in metres squared (kg/m^2), was used as one of the markers for vascular risk. Further details of how height and weight measurements were taken were not outlined in the study. BMI data was organised into cumulative quintiles and the population of headache sufferers in each quintile was assessed.
Variables	Headache status, headache severity/frequency, BMI and serum biomarkers such as: triglyceride levels, total cholesterol, C- reactive protein, etc.
Main results	Mean BMI was higher in children suffering headaches ($22.71kg/m^2$) compared with non-headache controls ($20.19kg/ m^2$). Generally across all age groups BMI values were higher among headache sufferers compared with non-headache controls. The prevalence of children with BMI in the highest quintile was 35% higher in headache sufferers compared with controls. Children with headaches were twice more likely to be in the highest BMI quintile (odds ratio= 2) compared with non-headache patients.
Bias and limitations	Information of basic headache status provided from the NHANES database did not distinguish between migraine and other specific variant headache causes. Hence this study did not establish a conclusion specific to migraine and adiposity. The NHANES study did not stipulate whether BMI was analysed based on percentiles or standardised z-scores. Results were adjusted for age, sex, ethnicity, socioeconomic status and the presence of co-morbidities such as asthma.

Table 1.1.7- Review of the Nelson et al (2010)[50] study using an adaptation of the STROBE review[42]

The above studies[39-41,46-50] aimed to investigate obesity as a risk factor for migraine and primary headaches. Although these studies demonstrated a relationship between obesity and migraine their study designs were not robust enough to establish the direction of causality between obesity and migraine. Thus it could be argued that migraine can act as a risk factor for obesity. This pilot study aimed to investigate whether paediatric migraine patients had higher adiposity levels because of higher levels of obesogenic eating behaviours in comparison to non-migraine paediatric headache patients. The concept of eating behaviours is now described in chapter 1.2.

Chapter 1.2

Eating behaviours and appetite

General concept of eating

Food ingestion is a behaviour that is subject to internal and external determinants[51]. Physiological homeostatic mechanisms represent one aspect of the internal factors that influence feeding[52]. The behaviour of eating can be viewed as part of a homeostatic mechanism to replenish and maintain energy stores, as supported by glucoprivation studies that evidence hypoglycaemia as a potent hunger stimulus[53]. However the obesity disorder undermines the concept of homeostatic appetite control, due to the accumulation of excessive adiposity levels that surpass the required quantum for energy replenishment[54]. Recent studies have highlighted the role of eating behaviours such as restrained, external and emotional eating that can lead to increased adiposity levels[55].

Eating behaviours can be determined by functions of psychological factors, emotional states, availability of environmental food cues, responsiveness to foods, the enjoyment of food, speeds of eating and food preferences[56]. In turn these factors are subject to influences from the perceived palatability of food, which forms one element of the reward gained from consuming certain foods[57]. Obesogenic eating behaviours result in hyperphagia that subsequently increase adiposity levels[58]. Key concepts surrounding eating behaviours are now discussed in this chapter.

Hedonic eating concept

The desire to eat is driven by the perceived rewards gained from eating[59]. This reward system consists of two parts: food hedonism ("like") and food motivation ("want")[60]. Motivation is the behavioural incentive and drive for pursuing a desired stimulus (i.e. "how much we want to eat a certain food item"). It can manifest in the form of cravings for particular foods with the perceived pleasures to be gained rated very highly[61]. The motivation to eat is mediated by the mesotelencephalic dopamine pathways, the nucleus accumbens and the amygdala[62].

The behaviour of eating is largely driven by the palatable pleasures gained from food consumption[63]. Hedonism is a concept of food intake stimulated by the perceived pleasures to be gained from food consumption[64]. Adiposity levels as measured by BMI are positively correlated with hedonism as measured by pleasantness ratings for food items[65]. Obese individuals share a heightened hedonic response to food, which is likened to the behaviour of compulsive gamblers and drug addicts that are pre-occupied with their habit even when not engaging in the activity. Similarly obese hedonistic eaters are shown to eat in the absence of hunger, without the need for food cues[66]. The activation of brainstem opioid and GABA receptors involved in the behaviour of addiction has been associated with increased levels of hedonistic eating behaviour[67].

In overview, the theory of reward is based on the desire to consume a food item (hedonism) and the decision of whether the motivation ("want") and effort to seek the reward is worthwhile[68]. Obese adults have been shown to work harder for a palatable reward than lean individuals, indicating obese subjects work harder for food rewards[69].

Emotional eating (psychosomatic theory)

States of anxiety, fear or anger are able to influence appetite. The physiological response to emotional arousal is the inhibition of gastric motility and the liberation of glucose from liver glycogen stores[70]. However some individuals lack interoceptive awareness and are unable to recognise whether they are hungry or satiated. As a result they overeat in response to any high emotional arousal, usually resulting in the over-consumption of high calorie energy dense foods; this phenomenon is known as "emotional eating" and has been positively correlated with adiposity[71].

Restrained eating

Continuous food restriction in people that diet initiates physiological defences in the form of lowered metabolic rate and the arousal of persistent hunger[72]. When self control is undermined by disinhibitors such as alcohol or emotional arousal (e.g. anger, anxiety, etc) the cognitive resolve to diet is abandoned and food is excessively consumed[73]; this phenomenon is known as "restrained eating". Restrained eaters have strong hedonistic drives for appetite, desensitised responses to internal satiety signals and higher adiposity levels compared with non-restrained eaters[74].

External eating (externality theory)

Recent literature highlights the importance of environmental influences on diet. Readily available and widely advertised energy dense high fat foods at affordable prices provide a constant exposure to food cues[75]. The theory of external eating states that certain people are more sensitive to external food cues than others, and eat in response to those stimuli, regardless of their internal state of hunger and satiety[76]. Overweight individuals are demonstrated to be hyper-responsive to external food related cues such as the sight or smell of food[77]. The provision of food cues has been shown to induce rapid rates of food ingestion which are associated with greater adiposity levels[78].

Children hedonistically respond to cues for food items that appear highly palatable, which can over ride internal satiety cues[79]. Energy dense food brands are widely advertised to millions through TV and radio marketing. Food brand organisations specifically target youths because of their spending power, purchasing influence and role as future adult consumers[80]. In recent decades children have developed a greater freedom in food choice with a common practice to eat outside the house or "on the go" which facilitates the development of external eating in a food cue rich environment[81].

Restrained, emotional, external and hedonistic eating behaviours are all associated with obesity and higher adiposity levels in children and adults[71,74,78,65]. Chapter 1.3 now outlines background information on adiposity and the obesity disorder.

Chapter 1.3

Obesity

Obesity definition and prevalence

The World Health Organisation (WHO) defines obesity as an abnormal or excessive level of adiposity that presents a risk to health[82]. Body mass index (BMI) is commonly used as an indirect measure of adiposity among large scale populations[83]. It is calculated by dividing a person's weight in kilograms by the square of their height in metres. In adults, a BMI value of greater than 25kg/m^2 indicates an individual is overweight and a value greater than 30kg/m^2 is an indicator of obesity[84].

It is estimated that up to 1.6 billion people worldwide are overweight, of which almost 400 million people are obese[85]. The WHO projects that by 2015, 2.3 billion adults may be at risk of becoming overweight with a constituent 700 million people at risk of becoming obese[86]. Fifty percent of adult obesity is suggested to stem from an early onset during early adolescence[87]. Paediatric overweight and obesity rates have accelerated in prevalence by 120% between years 1986 and 1998[88]. An amalgamation of global statistics in 2007 revealed that at least 20 million children under the age of 7 were overweight[85]. The UK prevalence of overweight children aged 2 to 5 years is 31% and 29% for males and females respectively[89]. The reported prevalence of overweight children in Liverpool is 27% among males and 31% among females[90]. By the year 2050 UK childhood obesity rates are estimated to rise by 19% and annual NHS weight related costs are anticipated to inflate by £15.8 billion as predicted by the foresight report[91].

Quality of life and obesity related morbidities

Huge health, fiscal and wider societal effects have accompanied the rapid global rise in obesity[92]. Severely obese children have a lower health related quality of life compared with normal weight controls[93]. Cancer patients reflect similar quality of life ratings as those for obese children. Increased parental distress, peer victimisation and depressive symptoms are associated with reports of low quality of life in obese children[94].

Excess weight gain at a young age increases the risk of obesity related morbidities in later adult life. Childhood obesity is associated with asthma, sleep apnoea and non-insulin dependent diabetes[95,96]. Other obesity related paediatric morbidities include orthopaedic problems such as Blount's disease (a growth disorder of the tibia), skin fungal infections and hepatic steatosis[97]. Obese children are at increased risk of psychological problems such as negative self esteem, social withdrawal, depression, anxiety and feelings of chronic rejection[98]. The development of such psychological issues overlaps with eating disorders and eating behaviours[99].

Obesity Mechanisms

As illustrated by figure 1.3.1, weight is determined by factors that affect energy intake and energy expenditure which are subject to specific brain mechanisms[100,101]. Up to 40% of the variation in BMI can be attributed to genetics and up to 60% can be attributed to environmental factors[102]. Some people are genetically predisposed to developing obesity when exposed to an environment which encourages weight gain, such as a sedentary lifestyle and the access to high calorie foods[103]. The rapid rate of increase in obesity prevalence suggests that the cause is more due to the changing environment rather than genetic pre-selection[104].

Multiple genes contribute to the manifestation of the obesity phenotype[105]. The BMI of 540 child adoptees followed up at adulthood was more similar to their biological parents than that of the adoptive carers[106]. Homozygous expression of the fat mass and obesity gene (FTO gene) is associated with higher adiposity levels compared with low risk alleles[107]. Messenger RNA from the FTO gene is expressed in the arcuate nucleus of the hypothalamus and has been shown to influence weight via alterations in appetite[108,109].

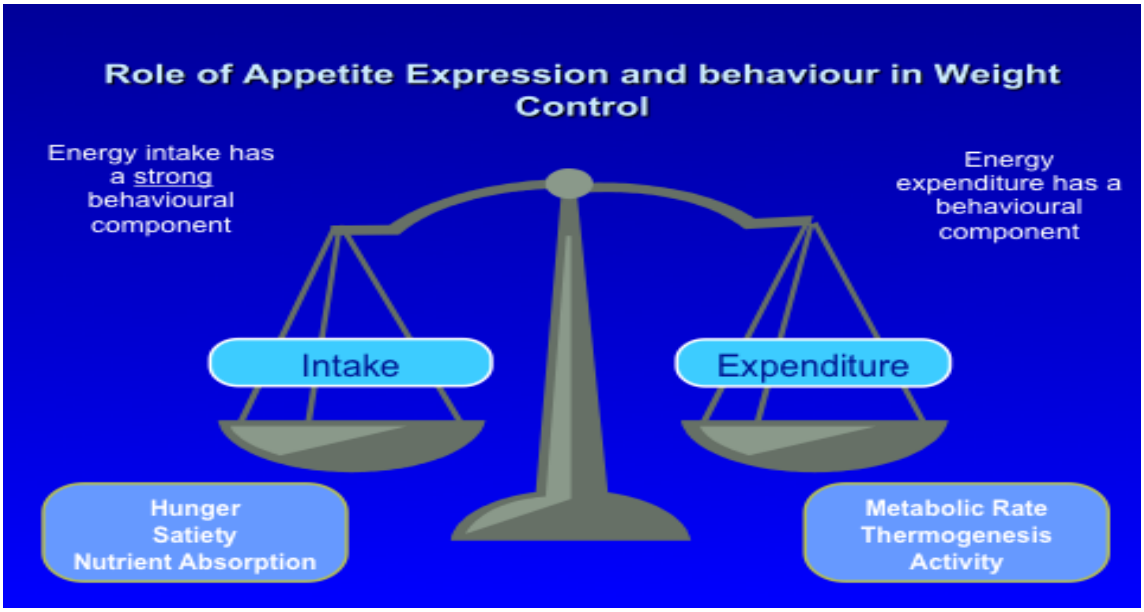


Figure 1.3.1 - Overview of energy balance (this diagram has been used with the permission of Liverpool University, Psychology Department)

Over the past few decades the western world has adopted a more sedentary life style that has progressively escalated to a state where energy output is very minimal and disproportionate to energy intake[110]. New advances in labour saving technology such as cars and computers have deterred people from physical activities that used to be part of everyday life[111]. There has been a shift from cooking fresh foods to fast food consumerism[112]. The importance of diet and energy expenditure as key determinants of adiposity levels[113] can be demonstrated by the Pima Indians that separated over 700 years ago with one colony settling in Arizona and the other settling in Mexico. The Arizona Pima Indians were exposed to a diet more rich in animal fats and simple sugars than the Mexican

Pima Indians, who had a more traditional lifestyle involving greater physical activity. Despite the genetic similarities, the difference in diet and lifestyle over time has led to a higher prevalence of obesity among the Arizona Pima Indians compared with the Mexican Pima Indians[114].

Eating behaviours that influence appetite are associated with obesity[56] and are regulated by hormonal and neural mechanisms[115]. Serotonin[116,117], calcitonin gene related peptide (CGRP)[118,119], orexins[120,121] and leptin[122,123] are hormones that share a common neurobiological overlap in both migraine and obesity pathologies. The hypothalamic areas involved in appetite regulation[124] have been linked to migraine pathology[125]. The neurobiological overlap between migraines, appetite and adiposity are now reviewed in the following chapter 1.4.

Chapter 1.4

Neurobiological overlap between migraines, appetite and obesity

Serotonin

Serotonin, also known as 5-Hydroxytriptamine (5-HT) is a mono-amine neurotransmitter primarily found in the gastrointestinal tract and central nervous system[126]. Low serum serotonin levels and high CSF (cerebrospinal fluid) concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), are found in migraine patients between acute attacks. Conversely during acute migraine attacks there are elevated plasma levels of serotonin and low serum concentrations of 5-HIAA[116]. This implies migraine is a chronic state of low serotonin availability with short bursts of serotonin increase during times of acute attacks.

Serotonin is a satiety inducer that forms part of a homeostatic mechanism that inhibits excessive food consumption[117]. Large serotonin deposits are found in the sub-oesophageal ganglia of leeches that function to regulate food ingestion and satiation[127]. Serotonin injections into hypothalamic nuclei that express 5-HT receptors significantly reduce appetite levels and increase eating speeds[117]. Given that migraine patients suffer from a chronic state of serotonin deficiency[116], there may be a lack of appetite regulation from serotonin and thus migraine patients may have larger appetite levels that in the long term could lead to increased adiposity levels[117].

Calcitonin Gene Related Peptide (CGRP)

CGRP is a 37 amino acid neuropeptide formed from the alternative splicing of the calcitonin/CGRP gene located on chromosome 11[128]. CGRP facilitates nociceptive transmission and has potent vasodilatory effects[129]. During acute migraine attacks there are elevated levels of serum CGRP found in the external jugular and cubital veins, as well increased concentrations of salivary CGRP[118]. Patients administered CGRP drug infusions can develop a late onset non-aura migraine headache[130]. Blockade of the CGRP receptor using the CGRP antagonist BIBN4096 has been shown to attenuate headache pain[131].

Precipitates of mRNA encoding CGRP are distributed along several brain areas important in eating behaviour[132]. The central administration of CGRP in animal models stimulates a ravenous appetite that can lead to excessive food consumption[119]. Serum CGRP concentrations are significantly higher among obese individuals compared with normal weight controls[133]. Fat ingestion is linked to CGRP secretion, a possible mechanism by which CGRP levels are associated with obesity[83]. Based on the information presented so far, migraine patients may develop larger appetite levels during acute migraine attacks (due to the increased secretion of CGRP) which in frequent occurrence could lead to high adiposity levels in the long term.

Orexins

Orexins are neuro-peptides formed from the proteolytic cleavage of the amino acid prepro-orexin. There are two isoforms, orexin A which acts on the orexin-1 receptor and orexin B which acts on the orexin-2 receptor[134]. The orexinergic system has broad projections to hypothalamic areas such as the periaqueductal grey and paraventricular nucleus[135]. In animal studies, the injection of orexin A causes a heightened appetite response and a slow satiety onset, with subsequent reversal of symptoms upon administration of the orexin-1 receptor antagonist[120]. The involvement of orexins in nociceptive processing has recently been implicated with evidence of orexin A showing analgesic properties in animal models[136]. Migraine patients have a significantly higher concentration of orexin A in their CSF fluid compared with matched controls[121]. The chronic pain state in migraine patients may stimulate a high release of orexin A as a compensatory mechanism to reduce pain levels[136] that in turn increases appetite and elevates adiposity levels[120].

Leptin

Leptin, a 16-kDA polypeptide hormone secreted from the adipose cells is a product of the OB gene, heavily involved in appetite regulation and metabolism[122]. Leptin profoundly raises bodily metabolic rate, increases thermogenesis and dramatically reduces appetite[137]. Leptin reduces appetite by sensitizing the brain to satiety signals from the stomach and duodenum[138]. Obese patients are thought to suffer from a state of “leptin resistance” where cells are unresponsive to the usual effects of leptin. It is likened to the underlying principle of non-insulin dependent diabetes. It is proposed that hypothalamic receptors become desensitised or leptin receptor density is down regulated, which ultimately leads to leptin resistance with increased food intake[139]. Migraine patients are subject to significantly low serum leptin levels when compared with healthy matched controls[123]. This last piece of evidence suggests that because migraine patients have low leptin levels they may be inclined to develop aberrant hyperphagic eating patterns which can result in higher adiposity levels[123,137].

The hypothalamus

The hypothalamus is involved in analgesic processing. Hypothalamic corticolimbic connections are implicated in the affective and cognitive aspects of pain perception[140]. Electrical stimulation of the paraventricular nucleus evokes anti-nociceptive effects[141]. Chronic migraine is associated with sleep disorders such as insomnia and narcolepsy that share a common pathology of hypothalamic dysfunction. The trigeminal pathway can act as a trigger for hypothalamic activation[142,143]. Positron emission tomography (PET) scanning has revealed clear hypothalamic activation during the early phases of acute migraine attacks[125].

The ventro-medial hypothalamus has a strong role in satiety. Localised lesions in this brain area can cause progressive weight gain through constant overeating patterns and the loss of metabolic control from connections with the paraventricular nucleus[124]. The lateral hypothalamus coordinates food seeking behaviour through metabolic hunger signalling and is heavily involved in the underlying mechanism of food reward. Isolated neuro-toxic lesions of the lateral hypothalamus result in a long term decrease in food intake with subsequent weight loss[144]. The lateral hypothalamus and the midline thalamus relay energy balance information to brain areas involved in behavioural action[145]; these areas are also involved in migraine pathology[100]. It is possible that migraineurs suffer from hypothalamic pathology that increases appetite levels and results in increased adiposity levels[124,125,144].

Chapter 1.5

Migraine and appetite

Migraine and food cravings/ binge eating

Food cravings (defined as an intense desire to consume a particular food item that is difficult to resist) can develop in migraine patients as part of a premonitory phase prior to the onset of an acute attack[146]. Although a physiological mechanism has not yet been identified, the ICHD-II delineates fasting and skipping meals as potential triggers for acute migraine attacks[1]. Blau et al demonstrated that 45% of migraine patients can still consume food in states of nausea during an acute migraine attack, which can actually shorten headache duration and alleviate symptoms of nausea[147]. Brewerton et al found that 59% of 34 female migraine patients exhibited binge eating behaviour according to the eating disorders inventory (EDI)[148]. Binge eating behaviour has also been shown to have a positive correlation with restrained eating[149] and adiposity[150]. It is possible that migraine patients with binge eating habits may also have restrained eating patterns which can cause greater adiposity levels to develop.

Migraine treatment and adverse weight altering effects

Topiramate, originally an anti-epileptic drug used to treat migraine is commonly associated with adverse weight loss[151]. Topiramate suppresses the lateral hypothalamus via its antagonistic effects on the kainite and glutamate receptors, whereby inducing an anorectic response with subsequent weight loss. In overview, topiramate suppresses hunger so that

appetite and food intake are reduced[152,153]. The use of pizotifen, another prophylactic anti-migraine medication, is of limited use in obese patients due to the potential adverse effect of weight gain. Maggioni et al found up to 86% of migraine subjects each gained a minimum of 4kg in weight after a 6 month pizotifen treatment period[154]. Pizotifen has an antagonistic effect on 5-HT_{2C} receptors which is believed to stimulate and increase appetite levels that cause subsequent weight gain[151]. No study has hitherto successfully elucidated the mechanism behind these weight altering adverse drug reactions, although current literature suggests that there is a disruption in appetite which is the key mechanism by which weight is affected.

Chapter 1.6

Conclusion

BMI as an indirect measure of adiposity is positively associated with migraine prevalence, migraine severity and headache frequency[39-41,46-50]. Restrained, emotional, externalised and hedonistic driven eating behaviours are strongly associated with increased adiposity levels and obesity development[71-81]. Migraine patients can develop food cravings during the prodromal and ictal phases of acute migraine attacks[1,146]. Particular migraine treatments, such as topiramate and pizotifen, can adversely alter weight through effects on appetite[151-154]. There is a substantial neurobiological overlap of serotonin, calcitonin gene related peptide (CGRP), orexin A, leptin and hypothalamic related pathology between migraines, appetite and adiposity[116-125]. As can be seen in figure 1.6.1, the direction of the relationship between migraines, eating behaviours and adiposity has not yet been established and requires further investigation.

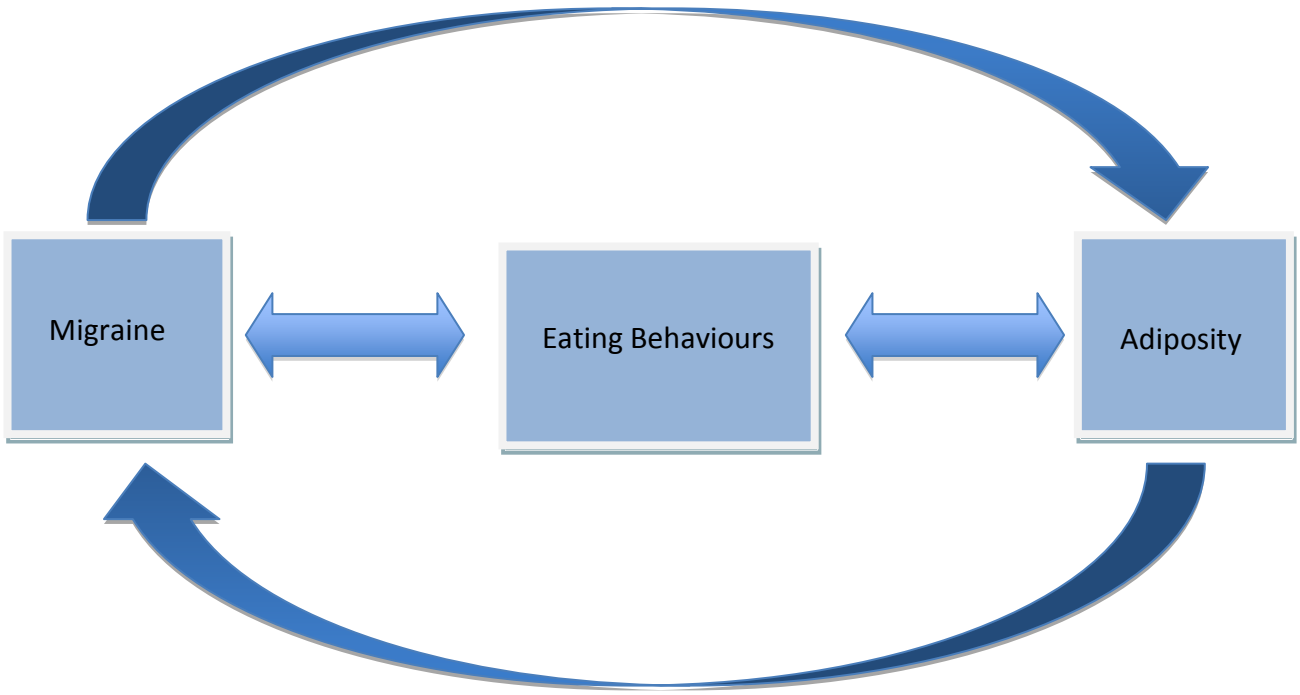


Figure 1.6.1
Diagram to outline the relationship between migraines, eating behaviours and adiposity

Based on the information presented so far, it is possible that a causal relationship may exist between migraines, eating behaviours and adiposity. However no study hitherto has investigated the relationship of all three variables together. Hence this pilot study was developed to investigate the relationship that migraine shares with eating behaviours and adiposity. The following section outlines the methodology used in this pilot study. This pilot study was also used to identify limitations in the methodology to help prepare for a larger future study on "migraines, eating behaviours and adiposity". This main future study will be designed to confirm and extend the findings from this present pilot study. Power sample size calculations for the main future study have been presented in this thesis.

Chapter 2.0

Study Methodology

It must be noted that the methodology for this pilot study was originally designed by a previous MPhil student from August 2008 to August 2009. The second researcher (the author of this thesis) took over the pilot study in August 2009 and made no contribution to designing the methodology of this pilot study. Instead the second researcher was mainly involved with the patient recruitment, data collection, data analysis and reporting process.

Chapter 2.1

Study Objectives

Primary objective:

- To assess whether eating behaviours differ between migraine cases and non migraine control headache patients.

Secondary objectives:

- To assess whether food cravings, food intake and adiposity levels differ between migraine cases and non migraine control headache patients.
- To assess the relationship eating behaviours, food cravings, food intake and adiposity levels have with migraine severity and monthly headache frequency among migraine cases.

- To assess the relationship behavioural issues have with eating behaviours, food cravings, food intake, adiposity levels, migraine severity and monthly headache frequency among migraine cases. This is to account for the confounding effects that behavioural issues may have on any relationships observed in the study.

- After this pilot study has been completed the final aim is to evaluate potential changes/improvements in the methodology for the main future study on "Migraines, Eating behaviours and Adiposity in children".

Chapter 2.2

Study Design

Overview of Study design

A single-centre, cross-sectional, questionnaire-based, clinical migraine population pilot study was designed. The primary outcome was to identify an association between measures of migraine severity and headache frequency with obesity related eating behaviours. The independent variables were monthly headache frequency and migraine severity as determined by the Paediatric Migraine Disability Assessment questionnaire (PedMIDAS). Eating behaviours were assessed using the Dutch Eating Behaviour Questionnaire for adolescents (DEBQ-adolescent version), the Children's Dutch Eating Behaviour Questionnaire (DEBQ-C) and the Child Eating Behaviour Questionnaire (CEBQ). Food cravings were evaluated by the Food Cravings Inventory (FCI-II) and food intake on the previous day was assessed using the Food Intake Questionnaire (FIQ). Adiposity was indirectly measured using BMI z-scores. Behavioural problems were evaluated using the Child Behaviour Checklist (CBCL). Local Research Ethics and Trust R&D approvals were granted in June 2009 for this pilot study to be conducted at Alder Hey Children's NHS Foundation Trust.

Patient sample

A major reason for conducting a pilot study is to determine what type and quantity of data is required to either prove or disprove a hypothesis, to assess the feasibility of patient recruitment and also to perform a sample size calculation for a larger study[155]. The number of patients to be included in a pilot study depends on the parameter(s) to be estimated[156]. Gillian et al conducted a study on the design and analysis of pilot studies and recommended using 30 patients or greater to estimate a parameter[157]. The degree of association between the measure of migraine severity and of restrained eating, emotional eating and external eating, respectively, were intended to be the 3 main parameters of focus in this pilot study. Hence following various discussions with a statistician, a total of 90 patients were decided as the target sample size; 60 migraine cases and 30 non migraine headache controls. It must be noted that the decision about the sample size was made by the previous researcher of this pilot study and the justification given is based on that of the previous researcher.

Patient recruitment

Headache referral patients aged 5 to 17 years were approached for recruitment at neurology outpatient clinics and general paediatric clinics at Alder Hey Children's Foundation Trust Hospital, Liverpool. The recruiting agent attended the patient's clinic consultation to gain confirmation of their headache diagnosis, which was then compared with a migraine pro-forma. Parents and children that were approached after the clinic were given general information on the pilot study and if interest for participation was expressed they were then briefed in more depth about the study in a private room. Fully informed consent was gained from the parent on the child's behalf. The relevant questionnaires were then administered and filled out. Usually an average of one hour was spent recruiting each patient in this manner.

Patients

Headache patients seen in clinic that were diagnosed with migraine by the treating clinician were approached for recruitment as migraine cases. Newly referred migraine patients aged 5 to 17 years were used as cases. Most of the migraine headache patients at Alder Hey neurology clinics and general paediatric clinics are commenced on prophylactic or acute rescue medication usually after their first clinic consultation. They are then usually followed up for review at clinic at a later date to assess whether the drug treatment was successful. By the time the patient has attended a follow up clinic the medication may have already taken effect on migraine neurobiology and also caused an alteration in weight if treated with pizotifen or topiramate. Therefore it was decided to focus on newly referred headache patients because in comparison to follow up patients they were less likely to be taking any prophylactic medication[151-154]. Headache patients aged 5 to 17 years not suffering from migraine or any secondary organically induced headaches, were targeted as control patients.

Patient exclusion criteria

Patients younger than 5 years were excluded. The maximal age of Alder Hey outpatients was 17 years and hence was also the maximal age of patients that could be recruited. Patients with a secondary organic cause (e.g. brain tumours) for their headaches were excluded from the study. Brain tumours are a very distinct category of disease associated with an over-expression of leptin receptors and appetite disturbances[158]. By excluding organic neurological disorders the control group could consist of patients with a similar neurobiology. It was necessary for patients to be drug naive, due to the possibility that certain prophylactic medications can affect weight through altered appetite behaviours[151-154] (see chapter 1.5: Migraine treatment and adverse weight altering affects).

Chapter 2.3

Questionnaire tools used in study

This study was conducted as a joint partnership between Consultant Neurologists based at Liverpool Alder Hey Children's Hospital and the Liverpool University Psychology appetite research team. The appetite research team were highly involved in the questionnaire tool selection process. The tools used in this pilot study are now outlined.

Assessment of eating behaviours

It was important to use a psychometric tool which accurately measured eating behaviours. Much of the literature on eating behaviours presented so far has been contributed and tested by the Dutch Eating Behaviour Questionnaire (DEBQ)[70-78]. Through rigorous background reading and literature searching the DEBQ was confirmed as a reliable and valid tool for measuring eating behaviours[159]. For these reasons the DEBQ was chosen as an appropriate measure for eating behaviours in this pilot study.

There are two versions of the DEBQ:

- Dutch Eating Behaviour Questionnaire for adolescents (DEBQ- adolescent version) for targeted for use in children aged 12 or older[160].
- Children's Dutch Eating Behaviour Questionnaire (DEBQ-C) targeted for use in children aged 7 to 12 years[161].

Both tools were used considering the inclusion criteria for age was 5 to17 years. It was predicted that some of the younger children may lack capacity to competently report on their own eating behaviours. In addition to this the DEBQ-C was not designed for children aged below 7 years. Thus after discussion with the appetite research team, it was decided to

incorporate a parent reported tool for assessing eating behaviours. In doing so both perspectives from the child and parent were acknowledged and eating behaviours were also measurable in children below 7 years. The Children's Eating Behaviour Questionnaire (CEBQ) was the tool of choice because of its robust structure, wide use and validated measure of eating behaviours[162]. The DEBQ (adolescent version), DEBQ-C and CEBQ are now discussed in more depth.

Dutch Eating Behaviour Questionnaire for adolescents (DEBQ- adolescent version)[160]

The Dutch Eating Behaviour Questionnaire for adolescents (DEBQ- adolescent version) measured the levels of emotional, external and restrained eating behaviours. It was designed for adults and adolescents aged at least 12 years. It consisted of 33 closed questions; 13 for emotional eating, 10 for external eating and 10 for restrained eating. "Do you have a desire to eat when depressed or discouraged" is an example emotional eating question that was used in the DEBQ (adolescent version). "If you see or smell something delicious, do you have the desire to eat" is an example external eating question that was used in the DEBQ (adolescent version). "Do you try to eat less at mealtimes" is an example restrained eating question that was used in the DEBQ (adolescent version)[160]. Each question was answered by ticking off an answer on a 5-point scale provided at the side of each question; never (1), rarely (2), sometimes (3), often (4) or always (5). The number in each bracket was the score given for the chosen option which allowed a quantitative analysis of the DEBQ[160].

The DEBQ has demonstrated excellent validity. All three sub-scales have featured a high level of reliability as reflected by the Cronbach's alpha scores; emotional (0.92), external (0.8) and restrained (0.95)[163]. The DEBQ has been widely used in various obesity and eating disorder studies in adults and adolescents[164].

Children's Dutch Eating Behaviour Questionnaire (DEBQ-C)[161]

The Children's Dutch Eating Behaviour Questionnaire (DEBQ-C) was developed to measure the levels of emotional, restrained and external eating patterns in children aged 7 to 12 years old. The items used in this tool were derived from the simplification of questions used in the DEBQ (adolescent version). It was tailored to the shorter attention span of younger children by limiting the tool to 20 questions. Answers were chosen from a simplified 3-point scale provided at the side of each question; "no (1)", "maybe (2)" or "sometimes (3)". The number in each bracket was the score given to the corresponding answer chosen, which allowed quantitative analysis of the DEBQ-C[161].

The DEBQ-C has demonstrated high reliability scores that range from 0.72 to 0.82. Cronbach's co-efficients at 0.8 for emotional eating, 0.68 for external eating and 0.72 for restrained eating have indicated high internal consistency of the scales[161]. As there were no reports of the DEBQ-C being used in any studies since its recent inception in 2008 this pilot study was the first to use the DEBQ-C outside of its initial development by Van Strien et al[77].

To allow the combined analysis of results from both the DEBQ (adolescent version) and DEBQ-C, the scores were adjusted for age and sex to produce standardised DEBQ z-scores. This was done on advice from the lead author of both the DEBQ (adolescent version) and DEBQ-C, Dr Tatjana Van Strien. The standardised DEBQ z-scores as opposed to the DEBQ (adolescent version)/DEBQ-C raw scores were used in the data analysis. In this thesis, it must be noted that the term DEBQ refers to data in the form of z-scores that were a collection of the DEBQ (adolescent version) and DEBQ-C raw scores.

The reference scores used to standardise the female DEBQ (adolescent version) scores were taken from a study on 724 Dutch secondary school girls aged between 12 to 16 years (mean age was 15.6 years and mean BMI was 20.1kg/m^2)[165]. The reference scores used to standardise the male DEBQ (adolescent version) scores were taken from a study on 104 Dutch secondary school boys aged 15 to 17 years (mean age was 17 years and mean BMI was 20.3kg/m^2)[73]. The reference values used to standardise the DEBQ-C scores were

extrapolated from the initial study in which the DEBQ-C was developed and validated. The sample consisted of 767 Dutch children (382 boys and 385 girls) aged 7 to 12 years with a mean age of 9.6 years[161].

Child Eating Behaviour Questionnaire (CEBQ)[166]

The child eating behaviour questionnaire (CEBQ) was a parent reported tool developed to assess 8 different domains of obesogenic eating behaviours in children aged 5-12 years. It consisted of 35 statements on food responsiveness (FR), emotional overeating (EOE), enjoyment of food (EF), desire to drink (DD), satiety responsiveness (SR), slowness of eating (SE), emotional under eating (EUE) and food fussiness (FF). Each statement was worded from the parent's perspective[166].

The food responsiveness (FR) subscale assessed how responsive the child is to eating, ("given the choice my child would eat most of the time" is an example FR statement that was used in the CEBQ). The emotional over eating and under eating subscales assessed whether the child over or under ate, respectively, in response to emotional stress. An example emotional overeating statement that was used in the CEBQ is "my child eats more when worried". An example emotional under eating statement that was used is "my child eats less when angry". The enjoyment of eating subscale assessed children's appetite by their desire and appreciation for food (an example statement that was used is "my child loves food"). The desire to drink subscale assessed general thirst levels (an example statement that was used is "if given the chance my child would always have a drink"). Satiety responsiveness determined children's sensitivity to internal satiety cues (an example statement that was used is "my child cannot have a meal after eating a snack"). The slowness of eating subscale assessed how quickly a child usually finishes their meal (an example statement that was used is "my child takes longer than 30 minutes to finish a meal". Food fussiness determined how selective a child was with their choice of foods (an example statement that was used is "my child refuses new foods at first")[166].

Parents had to choose from 5 options that best described how applicable statements in each CEBQ subscale were to their child. The options given per statement were; never (1), rarely (2), sometimes (3), often (4) or always (5). The number in each bracket represents the score given for each option to allow quantitative analysis of the CEBQ[166].

The CEBQ has demonstrated high test-retest reliability and high internal validity, as supported by its Cronbach's alpha scores; 0.56 (FR), 0.71 (EOE), 0.78 (EF), 0.82 (DD), 0.5 (SR), 0.57 (SE), 0.58 (EUE) and 0.7 (FF)[166]. The CEBQ has previously been used in a genetic study on the appetitive effects of the FTO gene on satiety responsiveness and enjoyment of food scales[58]. The CEBQ has been accepted as a suitable tool for use in studies measuring obesogenic eating behaviours[162].

It is important to note that the raw scores produced by the DEBQ (adolescent version) and DEBQ-C were not interchangeable or directly comparable with the CEBQ raw scores. Raw scores from the CEBQ were converted to standardised CEBQ z-scores. Reference scores used to standardise the CEBQ raw scores were based on the Wardle et al study[166] in which the CEBQ was initially developed and validated; it recruited 208 children aged 3 to 12 years old (mean age= 5 years). Instead of using the raw scores, the CEBQ subscale z-scores were used in the main statistical data analysis, because they were adjusted for age and sex.

Assessment of food intake

Following various discussions with the appetite research team it was important to assess what type of foods are eaten by migraine patients. The most accurate method would have been for each child to keep a food diary[167]. However this would have required following up patients for a second visit, which was an unfeasible prospect for recruiting 90 patients, considering the time limit in this pilot study[168].

There were a range of food frequency questionnaires (FFQ) which were also considered as potential measures of food intake. Different versions of the FFQ were able to assess what

types of specific foods are eaten and allow the calculation of nutrient intake[169]. However each available FFQ such as that used by Fumagalli et al[170] was presented in a complex format with a long list of questions which would have been difficult to understand and time consuming to answer for young children. While a food frequency questionnaire would have given more rigorous data with regards to nutrition[171], it was not necessary for the objectives in this pilot study.

Food Intake Questionnaire (FIQ)

The Food Intake Questionnaire (FIQ) was chosen to measure food intake because it was presented in a simple format for children to report on, it could be numerically graded which allowed quantitative analysis and it had a high content validity with respect to typical foods eaten on the previous day[172].

The FIQ, originally developed in the early 1980's, recorded the types of foods eaten on the previous day according to a set list of food items in the tool. It was designed to investigate the dietary habits of large numbers of school children. It asked "yesterday did you eat any amount of the following foods". Various foods were then listed at the end of this question and patients had to answer "yes (1)" or "no (0)" to whether they were eaten the day before. The number in each bracket was the score given for the answer chosen. It was the same scoring system as that used previously by Hackett et al[173]. This produced raw scores that were used in the FIQ data analysis.

Commonly eaten food items such as bread, cereal, chocolates, meats and dairy products were listed in the FIQ. The food items were broadly classified according to whether they were negative marker foods (unhealthy foods dieticians would recommend eating less of) or positive marker foods (healthy foods dieticians would recommend eating more of). The negative marker food items were divided into either negative marker sugary foods or negative marker fatty foods. Positive marker food items were categorised as foods that

were high in fibre (positive marker fibre foods) and those that were not[173]. This pilot study used FIQ negative marker food scores as a marker for the intake of unhealthy foods and FIQ positive marker food scores were used as a marker for the intake of healthy foods.

The FIQ has been used in various studies designed to explore the areas of diet that need improving in children[172]. When compared to a 3 day food diary the FIQ has displayed high criterion validity[174]. Thus even though the FIQ did not determine nutritional consumption, the food categories in the FIQ were representative of foods usually eaten by people. Results from the FIQ have been reproducible at 3 equal intervals over a 3 month period. The FIQ has also shown high face validity based on strong agreements between professional dietician opinions on foods considered as positive and negative markers[175].

The FIQ was designed for self completion by children aged 11 years or older. Although this pilot study intended to recruit children younger than 11 years, based on the simple format of the FIQ, it was decided to be age appropriate. Any children that struggled to understand the FIQ were given help by the parents or researcher. The question of whether alcohol was consumed on the previous day was not asked to children below the age of 11 years, as it was not appropriate.

Assessment of food cravings

As discussed in chapter 1.5 food cravings can develop during acute migraine attacks[147]. Hence it was important to address food cravings as an important hedonistic aspect to eating behaviours[60] in this pilot study. After detailed discussions with the appetite research team the Food Craving Inventory (FCI-II) was chosen to assess the strength of food cravings because it has been highly validated by previous obesity studies[176]. FCI-II Cronbach's alpha scores of 0.81 for high fats, 0.83 for sweets, 0.76 for carbohydrates and 0.7 for fast food fats suggested a high level of internal consistency and reliability[177].

Food Cravings Inventory (FCI-II)

The FCI-II was a self reported tool which listed 28 food items subdivided into 4 different food groups:

1. High fats (e.g.- fried chicken, sausages, etc)
2. Fast food fats (e.g.- pizza, chips, etc)
3. Carbohydrates (e.g.- pasta, cereal, etc)
4. Sweets (e.g.- cakes, chocolate, etc)

As described by Weingarten and Elston[178,179] cravings are "an intense desire to consume a particular food or food type that is difficult to resist". The Food Cravings Inventory (FCI-II) used this definition to ask whether in the last month there were cravings for any of the listed food items[178]. However to address the trait form of migraine the one month time frame was not applied and cravings were assessed generally over an unlimited time period. The patient had to choose from 5 options provided next to each food item which acted an indicator of the strength of craving; never (1) / rarely (2) / sometimes (3) / often (4) /always (5). The number in each bracket was the score given for the chosen option, which enabled a quantitative assessment of the strength of food cravings.

Assessment of Migraine severity and headache frequency

Trait versus State forms of migraine

Migraine patients suffer a chronic disease process which is the stable and diffuse form of migraine that can be regarded as a "trait". During bouts of acute migraine attacks the patients exhibit an immediate unstable form of the disease and are exhibiting the "state" form of migraine[180]. This concept of trait and state forms of disease can be applied to other

chronic conditions such as asthma. Asthmatics suffer from a disease pathology that is covert until overtly manifested through an acute asthma attack. Outside of these acute attacks there is still an active disease process present in a chronic but stable form which is only recognised or brought to light when expressed via an acute attack. The chronic underlying process of asthma is the "trait" form of asthma and the acute attacks are the "state" forms of asthma[181]. In exactly the same way migraine patients suffer from a disease pathology which is an on-going chronic but concealed "trait" process, the abnormality of which is only revealed during the onset of an acute migraine attack[180]. It was therefore important to measure migraine severity and monthly headache frequency using a tool that addressed the trait (chronic) form of migraine.

Deliberation of tool choice

The International Headache Society (IHS) scale would have assessed the effects of acute headache attacks on activities. However because this tool would have focussed on acute attacks it would not have accurately represented the trait form of migraine[182]. The number of rescue medications used by each migraine patient was another option for measuring migraine severity. However this was not feasible because of the exclusion criteria of any prophylactic medications. The headache Impact Test 6 score (HIT-6) was a six item questionnaire which assessed headache effects on usual activities, social functioning, cognition and emotional distress. However the HIT-6 was chosen because it had never been used in paediatric subjects and was very expensive to purchase[183]. The Paediatric Quality of Life tool would have assessed levels of disability, but was not selected because it focused largely on quality of life rather than migraine severity and did not measure headache frequency[184]. Ultimately the PedMIDAS questionnaire was chosen because it was cheap, quick to administer, easily understood by young children and it measured migraine severity as the trait form of migraine[185].

Paediatric Migraine Disability Assessment Scale (PedMIDAS)[185]

The Paediatric Migraine Disability Assessment Score (PedMIDAS) assessed the effect of headaches on activities of daily living. It was derived from the adult Migraine Disability Assessment Score (MIDAS), extensively used in migraine research. The PedMIDAS consisted of 6 questions that are outlined in table 2.3.1[185].

Question No	PedMIDAS question
1	How many full school days were missed in the last 3 months due to headaches?
2	How many partial days of school were missed in the last 3 months due to headaches?
3	How many days in the last 3 months did you function at less than half your ability in school because of headaches?
4	How many days were you not able to do things at home (i.e. chores, homework, etc) due to headaches?
5	How many days did you not participate in other activities (i.e. play, go out, sports, etc) due to headaches?
6	How many days did you participate in these activities but functioned at less than half your ability due to headaches?

Table 2.3.1- Questions from the PedMIDAS tool

The number of days answered for each question were all added together to produce a total PedMIDAS score, which this pilot study used as a measure of migraine severity. As outlined in table 2.3.2, a grading system based on PedMIDAS score cut off limits as adapted from Hershey et al, was used to categorise patients into one of four migraine severity grades[186]. The PedMIDAS also measured the number of headaches in the last 3 months which was divided by three to produce a monthly headache frequency value. As outlined in table 2.3.3, a grouping system adapted from Katsarava et al was used to categorise patients into one of three monthly headache frequency groups[187].

The PedMIDAS has been used as a migraine severity measure in 2 prior headache studies by Hershey et al. The first investigated the role of topiramate treatment in migraine[188] and the

second researched the influence of obesity on headaches[47]; both studies reported the tool as a valid measure of migraine disability. The PedMIDAS tool has shown high test-retest reliability (r= 0.8) and has been reported as a valid measure of headache severity when compared with self reported and clinician assessed headache severity scales[185]. The PedMIDAS measured overall functional disability rather than just the effects from acute attacks[186] and for this reason the PedMIDAS was appropriate as a measure of migraine severity in the chronic trait form of migraine.

PedMIDAS categories	Severity scale	Total PedMIDAS scores
Grade 1	Little to nothing	0 to 10
Grade 2	Mild	11 to 30
Grade 3	Moderate	31 to 50
Grade 4	Severe	> 50

Table 2.3.2- The four migraine severity grades classed according to the total PedMIDAS scores[32]

Category	Monthly headache frequency
Group 1	0 to 4
Group 2	5 to 10
Group 3	>10

Table 2.3.3- The three groups of monthly headache frequency

Migraine pro-forma and migraine classification

A migraine pro-forma was designed specifically for this pilot study to check whether migraine cases fulfilled a systematic criterion for a migraine diagnosis. This pro-forma was adapted from two sources of diagnostic criteria, a book by Guidetti et al called "Headache and Migraine in Childhood and Adolescence"[189] and the International Classification of Headache Disorders (ICHD-II)[1]. The pro-forma assessed the duration, frequency and intensity of acute headache attacks, exacerbating and relieving headache factors and the

presence of associated symptoms such as nausea, vomiting, photophobia and phonophobia. The presence of any aura symptoms and family history of migraine were also assessed. This pilot study used the same criteria as the ICHD-II[1] to class migraine cases as either "migraine headache without aura" or "migraine headache with aura". See appendix in chapter 5.1.3 for a copy of the pro-forma used in this pilot study.

Behavioural problems: Child Behaviour Checklist (CBCL)[190]

The child behaviour checklist (CBCL) was a parent reported psychometric tool that assessed psychological difficulties in children aged 4 to 18 years. The first section of the CBCL assessed the child's social competence by their ability to socialise with friends and siblings, and take part in school and extracurricular/sport activities. The second section of the CBCL consisted of a series of statements about whether the child suffered from internalising and externalising behavioural problems. The parent had to choose from a list of 3 options that described how applicable the statement was to their child; these options included "not true (0)", "somewhat/sometimes true (1)" or "very true/often true (2)". The number in each bracket was the score given for the answer chosen to allow a quantitative analysis of the CBCL[190].

Internalising problems were symptoms that the child may have experienced such as anxiety, depression, withdrawal or somatic complaints. An example internalising statement was "my child feels worthless or inferior". Externalising problems were the overt manifestations of internal issues, such as rule breaking or aggressive behaviour. An example externalising statement was "my child argues a lot"[190].

The CBCL raw scores were converted to standardised age and sex adjusted T-scores. The T-scores were based on CBCL scores obtained from a normative sample of 2,368 non-handicapped children aged 4 to 18 years. T-scores produced from this pilot study were

assessed for whether they fitted the profile of normal, subclinical and clinical behavioural problems[190].

Emotional and behavioural problems are associated with childhood migraine. In a cohort of 47 paediatric migraine patients, maternal CBCL reports for internalising T-scores were significantly higher among migraineurs compared with controls, 57.18 (S.D 10.15) Vs 49.84 (S.D 8.83), respectively, p = 0.001[191]. Obesity and adiposity are associated with childhood behavioural problems. In a cohort of 155 children, internalising CBCL T-scores in obese cases with higher adiposity levels were much higher than non-obese controls, 58.9 (10.9 S.D) Vs 55.4 (10.4 S.D), respectively. Externalising T-scores were 52.6 (SD 10.6) for obese individuals with higher adiposity levels and 48.1.1 (9.5 S.D) for controls[192]. These studies indicated that behavioural problems are associated with migraine, adiposity and obesity. Hence when designing the pilot study behavioural problems were recognised as a potential confounding factor between migraines, adiposity and obesity; so following discussions with the appetite research team it was decided to implement a measurement tool for measuring behavioural issues.

Psychiatrists have previously recognised the CBCL as a clinically meaningful tool with high validity. Confirmatory factor analysis has demonstrated that the factor structure of a clinician reported CBCL and parent reported CBCL are closely related[193]. Test–retest reliability correlations for the total CBCL T-scores are between 0.82 and 0.95, reflecting good reliability[194]. The CBCL has been extensively used in previous studies on migraines and obesity[89,90]. For these reasons the CBCL was implemented in this pilot study for measuring behavioural problems.

Measurement of adiposity

Magnetic resonance imaging (MRI), computed tomography (CT) and dual x-ray absorptiometry (DXA) were considered very accurate measures of adiposity. However these methods would have been unsafe in paediatric research, expensive and required expert handling.[195]. Bioelectrical impedance analysis (BIA) was another potential method for measuring adiposity; it would have estimated levels of body fat by measuring the oppositional flow of electrical current through body tissue[196]. A specific BIA instrument would have been required which was not purchasable due to limited funding. It was found that some BIA equations provided inaccurate estimates of body fat composition in obese patients[197]. Factors that could have biased BIA readings such as body position, skin temperature, previous exercise and food intake would have needed to be controlled[198]; which was not possible in this pilot study. Although other methods for determination of body composition may have provided more accurate estimates of body fat, BMI was safe, simple, inexpensive to obtain and highly validated based on its wide use to characterize child adiposity levels in large-scale epidemiologic studies[199].

Skin fold thickness was another technique considered for adiposity measurement. Skin fold thickness measurements taken from the triceps, calf or sub-scapular region would have needed to be converted by age and gender specific equations to produce body fat estimates.[200] It was found that some equations had not been validated and those that were, still produced body fat estimations that differed from those produced by gold standard DXA or CT scans[201]. Cohn et al found estimates of body fat from skin fold measurements to have a weak correlation with that of total body nitrogen composition (used as a determinant of fat free body mass and hence also fat mass)[202]. Janz et al were unable to cross validate the Slaughter equation based on triceps and calf skin fold thickness estimates in children[203]. A skin fold calliper would have been very sensitive to inter and intra user variability because skin folds can be easily over or under compressed[128]. Changes in body fat distribution according to pubertal development could have biased skin fold measurements, especially in young girls[204]. For these reasons skin fold callipers were not used to measure adiposity.

Body Mass Index

In children aged 5 to 19 years, BMI (kg/m^2) is highly correlated with total body fat mass as measured by dual energy x-ray absorptiometry (r = 0.85 for girls and 0.89 for boys)[205]. BMI as an indirect measure of adiposity is practical, easy to obtain, reliable and has been extensively used in various obesity studies[206]. For these reasons BMI was implemented an appropriate measure of adiposity with regards to the aims of this pilot study.

Higher readings of BMI signify higher levels of adiposity[205]. Body mass Index (BMI) was measured for each and every patient recruited into this pilot study; it was calculated as weight in kilograms divided by height in metres squared (kg/m^2). Height (cm) and weight (kg) measurements were routinely taken for all patients attending neurology and general paediatric clinics at Alder Hey hospital. Roughly 10 minutes before their appointment was due, the healthcare worker on duty for the clinic would call the patient into a private room to take height and weight measurements. A stadiometer was used to measure height in centimetres; the child would remove their shoes and socks, and stand with a straight posture with their eyes parallel to the floor. Weight was measured using standard weighing scales; the child would remove their shoes and socks, as well as any excess layers of clothing such as a coat. Height and weight measurements were documented in the patient's case files, which were then reviewed after the patient left the clinic to calculate BMI.

Based on their raw BMI value each patient was grouped according to a BMI status of normal weight, overweight or obese. The BMI groups were adapted from a study by Cole et al that developed age/sex adjusted international cut off points for raw BMI values that corresponded with overweight and obesity, based on a sample of 97,876 males and 94,851 females aged 0 to 25 years[207]. In this pilot study raw BMI values were converted to standardized z-scores so that were adjusted for age and sex. The BMI z-scores were calculated using reference values retrieved from the same study by Cole et al[155] that developed the BMI groupings.

Outcome	Questionnaire/ tool	Subscale
Migraine severity/ headache frequency	PedMIDAS (Paediatric Migraine Disability Assessment Score): All ages(child reported)	Total PedMIDAS score (migraine severity)
		Monthly headache frequency
Eating behaviours	Dutch Eating Behaviour Questionnaire for adolescents (DEBQ- adolescent version): 12+ years (child/patient reported) Children's Dutch Eating Behaviour Questionnaire (DEBQ-C): 7 – 12 years (child reported)	Emotional eating
		External eating
		Restrained eating
	Children's Eating Behaviour Questionnaire (CEBQ): 5- 12 years (parent reported)	Food Responsiveness (FR)
		Emotional Over Eating (EOE)
		Enjoyment of Food (EF)
		Desire to Drink (DD)
		Satiety Responsiveness (SR)
		Slowness of Eating (SE)
		Emotional Under Eating (EUE)
		Food Fussiness (FF)
Food cravings	Food Craving Inventory (FCI-II): 5-16 years (child reported)	High Fats
		Sweets
		Carbohydrates
		Fast food fats
Food Intake	Food Intake Questionnaire (FIQ): (child reported)	Negative Marker foods
		Negative Sugary foods
		Negative Fatty foods
		Positive marker foods
		Positive Fibre foods
Behavioural issues	CBCL (Child Behaviour Checklist): 1.5-5 years and 6-18 years (parent reported)	Internalising Behaviours
		Externalising Behaviours
		Total behaviours (Internalising and Externalising combined)
Adiposity	Body Mass Index (BMI)	Raw BMI values and BMI z-scores

Table 2.3.4- Summary of questionnaires used in this pilot study

Chapter 2.4

Statistical Data Analysis

Parametric distribution of data

Data produced for each variable in this pilot study was assessed for whether it was of parametric or non-parametric distribution. This was done via the following steps:

1. Skewness scores were calculated for each data set.
2. The standard error of the skewness score was calculated for each data set.
3. The skewness score was divided by its standard error.

A value greater than 1.96 indicated the data set was non-parametric and thus any statistical analysis done on this data set required use of a non-parametric test. A value less than 1.96 indicated that the data set was parametric and thus any statistical analysis done on this data set required a parametric test.

Statistical analysis

This pilot study intended to perform three main types of statistical analyses:

1. Data produced from each subscale of the DEBQ, CEBQ, FIQ and FCI-II, and BMI z-scores were intended to be compared between migraine cases and non-migraine headache controls. If data for both the migraine cases and controls were of parametric distribution, then an unpaired two-sample t-test would have been used to compare data. If one of the data sets being compared was of a non-parametric distribution then a Mann-Whitney U test would have been used to compare data.

2. The following correlations were intended to be performed:

    - The correlation that PedMIDAS scores have with each subscale of the DEBQ, CEBQ, FIQ, FCI-II, CBCL and BMI z-scores.

    - The correlation that monthly headache frequency values have with each subscale of the DEBQ, CEBQ, FIQ, FCI-II, CBCL and BMI z-scores.

    - The correlations that the CBCL subscale T-scores have with each subscale of the DEBQ, CEBQ, FIQ, FCI-II and BMI z-scores.

    The Pearson's correlation test would have been used if both the data sets being analysed were of a parametric distribution. The Spearman's rank correlation test would have been used if one or both of the data sets being analysed were of a non-parametric distribution.

3. Data produced from each subscale of the DEBQ, CEBQ, FIQ and FCI-II, and BMI z-scores were intended to be compared between the four migraine severity grades and between the three monthly headache frequency groups. If the data being compared was of a parametric distribution then the ANOVA (analysis of variance) test was used for statistical analysis. If the data being compared was of a non-parametric distribution then the Kruskal-Wallis test was used for statistical analysis.

If data for one of the subscales in a questionnaire was non-parametrically distributed then a non-parametric test was performed for each and every subscale of that questionnaire tool. For example if data (z-scores) for the restrained eating subscale of DEBQ was of a non-parametric distribution then any statistical analyses performed on all three subscales of the DEBQ would be done using non-parametric tests. All statistical tests in this pilot study were performed using Statistical package for the Social Sciences computer software (SPSS).

False discovery correction test

A probability level below or equal to 0.05 ($p \leq 0.05$) was considered to statistically significant for rejecting the null hypothesis in the statistical tests. This pilot study conducted multiple tests, which increased the probability of finding a significant result. Hence it was decided that to help resolve this issue a false discovery correction test must be applied to correct and lower the probability level (p-value) of statistical significance. The Bonferroni correction test was chosen because it was the most stringent type of correction test with respect to reducing the risk of making any false positive discoveries[208]. The Bonferroni test corrected the p-value by dividing the probability value (0.05) by the number of tests performed for a specific outcome measure. The corrected p-values were calculated only for the tests that compared data between the four PedMIDAS based migraine grades and between the three headache frequency groups. The probability values for the correlation tests were not corrected because the size of the correlation coefficient was the main focus of the correlation test, rather than the probability value. This was done on the advice from the statistician. In this pilot study the corrected p-values were calculated as follows: With respect to the outcome variable the number of subscales in a questionnaire was totalled.

This total was multiplied by two (one for each of the measures of migraine severity and headache frequency) to give the total number of statistical tests performed requiring correction. The end product of this calculation was then divided into the uncorrected p-value of 0.05), which then produced the final corrected p-value. See table 2.4.1 for corrected p-value calculations.

Variable	Questionnaire/ Outcome measure	No. of subscales in questionnaire/ assessment method	No. of variance tests done for each subscale	No. of variance tests done for each questionnaire	Corrected P-value for variance test
Eating behaviour	DEBQ (adolescent and child version combined)	3	2	(3x2)= 6	(0.05/6)= 0.008
Eating behaviour	CEBQ	8	2	(8x2)= 16	(0.05/16)= 0.003
Food intake	FIQ	5	2	(5x2)= 10	(0.05/10)= 0.005
Food cravings	FCI-II	4	2	(4x2)= 8	(0.05/8)= 0.006
Adiposity	BMI z-scores	1	2	(1x2)= 2	(0.05/2) = 0.025

Table 2.4.1 Outline of corrected p-value calculations.

Chapter 2.5

Intended hypotheses for study results

Restrained, external and emotional eating as measured by the DEBQ (adolescent version)[209] and DEBQ-C[161] are each positively correlated with adiposity. The FR, EOE, EF and DD subscales of the CEBQ are all positively correlated with adiposity, whilst SR, SE, EUE and FF subscales of the CEBQ are negatively correlated with adiposity[166]. Adiposity measured by BMI is positively correlated with migraine severity and headache frequency (see previous review of studies on headache obesity relationships[39-41,46-50]).

The consumption of unhealthy foods that have a high sugar and/or fat content is associated with adiposity[210]. In this pilot study the FIQ negative marker food scores were used as a marker for the intake of unhealthy foods (on the previous day) and FIQ positive marker food scores were used as a marker for the intake of healthy foods (on the previous day)[174]. Food cravings are associated with adiposity[211] and migraine[147]. Behavioural problems are associated with migraines, eating behaviours and obesity[126, 127].

Given this information the following hypotheses were generated:

- Compared with controls, migraine cases will have significantly higher:
    - DEBQ restrained/ emotional/ external eating z-scores
    - FR, EOE, EF and DD subscale z-scores of the CEBQ
    - FIQ scores for the intake of unhealthy foods (negative marker, negative sugary, negative fatty foods)
    - FCI-II scores for high fat foods, sweets, carbohydrates and high fat fast foods
    - BMI z-scores

- Compared with controls, migraine cases will have significantly lower:
    - SR, SE, EUE and FF subscale z-scores of the CEBQ
    - FIQ scores for the intake of healthy foods (positive marker and positive fibre foods)

- Migraine severity (PedMIDAS scores) and monthly headache frequency will each have a significantly positive correlation with:
    - DEBQ restrained/ emotional/ external eating z-scores
    - FR, EOE, EF and DD subscale z-scores of the CEBQ
    - FIQ scores for the intake of unhealthy foods (negative marker, negative sugary, negative fatty foods)
    - FCI-II scores for high fat foods, sweets, carbohydrates and high fat fast foods
    - BMI z-scores

- Migraine severity (PedMIDAS scores) and monthly headache frequency will each have a significantly negative correlation with:
    - SR, SE, EUE and FF subscale z-scores of the CEBQ
    - FIQ scores for the intake of healthy foods (positive marker and positive fibre foods)

- The following variables will significantly differ between the four migraine severity grades and will also significantly differ between the three monthly headache frequency groups:
    - All of the DEBQ subscales z-scores (restrained/ emotional/ external eating)
    - All of the CEBQ subscale z-scores (FR/EOE/EF/DD/SR/SE/EUE/FF)
    - All of the FIQ subscale scores (negative marker/negative sugary/negative fatty/ positive marker/positive fibre foods)
    - All of the FCI-II subscale scores (high fat/sweets/carbohydrates/high fat fast foods)
    - BMI z-scores

- CBCL subscale T-scores (internalising/externalising/total) will have a significantly positive correlation with:
    - Migraines severity (pedMIDAS scores)
    - Monthly headache frequency
    - DEBQ restrained/ emotional/ external eating z-scores
    - FR, EOE, EF and DD subscale z-scores of the CEBQ
    - FIQ scores for the intake of unhealthy foods (negative marker, negative sugary, negative fatty foods)
    - FCI-II scores for high fat foods, sweets, carbohydrates and high fat fast foods
    - BMI z-scores

- CBCL subscale T-scores (internalising/externalising/total) will have a significantly negative correlation with:
    - SR, SE, EUE and FF subscale z-scores of the CEBQ
    - FIQ scores for the intake of healthy foods (positive marker and positive fibre foods

Chapter 3.0- Results

Chapter 3.1

Distributions of study variables

As outlined from table 3.1.1, data for the total PedMIDAS scores were not normally distributed. Any analyses performed with the PedMIDAS scores had to be in the form of non-parametric tests. Hence all of the correlations made with the total PedMIDAS scores were done using the Spearman's rank correlation test (see table 3.1.2). Data for the monthly headache frequency values followed a parametric distribution. However given that the data for monthly headache frequency and PedMIDAS scores were intended to be analysed using the same type of statistical tests, all analyses performed with the monthly headache frequency data were also done using non-parametric tests; Hence all correlations made with monthly headache frequency were done using the Spearman's rank correlation test (see table 3.1.2).

Data for the four migraine severity grades and three monthly headache frequency groups followed a parametric distribution. This indicated that if a variable were compared between these migraine groups, a parametric test could be used on the condition that the data for the variable being compared also followed a parametric distribution. It must be noted that the same type of statistical test (based on whether it was parametric or non-parametric) had to be used for each subscale from the same questionnaire. Hence if one subscale from a questionnaire produced non-parametric data, then all subscales would need to be analysed using a non-parametric test. With this in mind, as outlined in table 3.1.1, at least one subscale from each of the main questionnaires used in this pilot study (DEBQ, CEBQ, FCI-II and FIQ) produced data that was of a non-parametric distribution. Thus data from each subscale of the DEBQ, CEBQ, FCI-II and FIQ were compared between the four migraine

severity grades and between the three headache frequency groups using the Kruskal-Wallis test (see table 3.1.3). It also meant that the same variables were correlated with the CBCL subscale T-scores using the Spearman's rank correlation test.

Data for the BMI z-scores followed a parametric distribution. For this reason, BMI z-scores were correlated with CBCL subscale T-scores using the Pearson's correlation test and were compared between the four migraine severity grades and between the three monthly headache frequency groups using the ANOVA analysis.

Variable	Parametrically Distributed?
PedMIDAS scores	No
Monthly headache frequency	Yes
Four migraine severity grades (I, II, III and IV)	Yes
Three monthly headache frequency groups (1, 2 and 3)	Yes
BMI Z-scores	Yes
DEBQ Emotional Eating Z-score	No
DEBQ External eating Z-score	Yes
DEBQ Restrained eating Z-score	No
CEBQ Food Responsiveness (FR) Z-score	Yes
CEBQ Emotional Over Eating (EOE) Z-score	No
CEBQ Enjoyment of Food (EF) Z-score	Yes
CEBQ Desire to Drink (DD) Z-score	Yes
CEBQ Satiety Responsiveness (SR) Z-score	Yes
CEBQ Slowness of Eating (SE) Z-score	Yes
CEBQ Emotional Under Eating (EUE) Z-score	Yes
CEBQ Food Fussiness (FF) Z-score	Yes
FCI-II High Fats raw scores	Yes
FCI-II Sweets raw scores	No
FCI-II Carbohydrates raw scores	Yes
FCI-II Fast Food Fats raw scores	Yes
FIQ- NEG- Food Markers raw scores	No
FIQ- NEG- Sugary Food Markers raw scores	Yes
FIQ-- NEG- Fatty Food Markers raw scores	No
FIQ- POS+ Food Markers raw scores	Yes
FIQ- POS+ Fibre Food Markers raw scores	No
CBCL Externalising T-scores	Yes
CBCL Internalising T-scores	Yes
CBCL Total T- scores	Yes

Table 3.1.1- Parametric status of data collected on the various study outcome measures

Variable	PedMIDAS scores	Monthly headache frequency
BMI Z-scores	Spearman's rank	Spearman's rank
DEBQ Emotional Eating Z-score	Spearman's rank	Spearman's rank
DEBQ External eating Z-score	Spearman's rank	Spearman's rank
DEBQ Restrained eating Z-score	Spearman's rank	Spearman's rank
CEBQ Food Responsiveness (FR) Z-score	Spearman's rank	Spearman's rank
CEBQ Emotional Over Eating (EOE) Z-score	Spearman's rank	Spearman's rank
CEBQ Enjoyment of Food (EF) Z-score	Spearman's rank	Spearman's rank
CEBQ Desire to Drink (DD) Z-score	Spearman's rank	Spearman's rank
CEBQ Satiety Responsiveness (SR) Z-score	Spearman's rank	Spearman's rank
CEBQ Slowness of Eating (SE) Z-score	Spearman's rank	Spearman's rank
CEBQ Emotional Under Eating (EUE) Z-score	Spearman's rank	Spearman's rank
CEBQ Food Fussiness (FF) Z-score	Spearman's rank	Spearman's rank
FCI-II High Fats raw scores	Spearman's rank	Spearman's rank
FCI-II Sweets raw scores	Spearman's rank	Spearman's rank
FCI-II Carbohydrates raw scores	Spearman's rank	Spearman's rank
FCI-II Fast Food Fats raw scores	Spearman's rank	Spearman's rank
FIQ- NEG- Food Markers raw scores	Spearman's rank	Spearman's rank
FIQ- NEG- Sugary Food Markers raw scores	Spearman's rank	Spearman's rank
FIQ-- NEG- Fatty Food Markers raw scores	Spearman's rank	Spearman's rank
FIQ- POS+ Food Markers raw scores	Spearman's rank	Spearman's rank
FIQ- POS+ Fibre Food Markers raw scores	Spearman's rank	Spearman's rank
CBCL Externalising T-scores	Spearman's rank	Spearman's rank
CBCL Internalising T-scores	Spearman's rank	Spearman's rank
CBCL Total T- scores	Spearman's rank	Spearman's rank

Table 3.1.2- Correlation tests used in analysis according to parametric status of data

Variable	PedMIDAS migraine severity grades	Monthly headache frequency groups
BMI Z-scores	ANOVA test	ANOVA test
DEBQ Emotional Eating Z-score	Kruskal-Wallis test	Kruskal-Wallis test
DEBQ External eating Z-score	Kruskal-Wallis test	Kruskal-Wallis test
DEBQ Restrained eating Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Food Responsiveness (FR) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Emotional Over Eating (EOE) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Enjoyment of Food (EF) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Desire to Drink (DD) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Satiety Responsiveness (SR) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Slowness of Eating (SE) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Emotional Under Eating (EUE) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
CEBQ Food Fussiness (FF) Z-score	Kruskal-Wallis test	Kruskal-Wallis test
FCI-II High Fats raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FCI-II Sweets raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FCI-II Carbohydrates raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FCI-II Fast Food Fats raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FIQ- NEG- Food Markers raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FIQ- NEG- Sugary Food Markers raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FIQ-- NEG- Fatty Food Markers raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FIQ- POS+ Food Markers raw scores	Kruskal-Wallis test	Kruskal-Wallis test
FIQ- POS+ Fibre Food Markers raw scores	Kruskal-Wallis test	Kruskal-Wallis test

Table 3.1.3- Type of test used to compare a variable between the migraine groups according to whether or not the data was of a parametric distribution

Study participants

A total of 83 consecutive new referral migraine patients and 10 control non-migraine headache patients were approached for recruitment into this pilot study. However of the 93 patients approached only 67 patients in total were successfully recruited (60 migraine cases and 7 controls). The other 26 patients were unable to take part because of parental time constraints, i.e. the parents were unable to give up 45-60 minutes for the recruitment process. Data collected for the 7 control patients were not used in the final results analysis because the sample size was too small to enable accurate statistical judgments on hypothesis testing. Hence this pilot study was unable to meet the primary and secondary objectives to compare eating behaviours, food intake, food cravings and adiposity between migraine cases and controls. The results analysed in this pilot study were based solely on the 60 migraine cases recruited.

Category	Characteristic	N	% (of N = 60)
Gender	*Female*	34	57
	Male	26	43
Age	*Patients aged 5 to 12 years*	37	62
	Patients aged 13 to 16 years	23	38
BMI status	*Normal weight*	46	77
	Overweight	9	15
	Obese	5	8
Race	*Caucasian*	58	97
	*Mixed Race**	2	3
Diagnosis	*Migraine*	60	100
	Non-migraine (Control)	0	0

Table 3.1.4- Patient characteristics. *Non-Caucasian patients did not state their specific ethnicity, but instead broadly stated that they were mixed race.

The ratio of male to female patients recruited was 26:34. Other studies have reported migraine prevalence at a 2:3, male to female ratio[12]. The youngest and eldest patients recruited were 6 years and 16 years, respectively. As can be seen from table 3.1.4, there was a larger proportion of children aged 5 to 12 years (n=39), compared with children aged 13 to 16 years (n=21). The majority of the patients were of normal weight (n= 46) and only 5 patients were actually obese.

Chapter 3.2

Migraine results

Migraine characteristics

As can be seen from table 3.2.1 the majority of patients were diagnosed as migraine with aura (n= 41, 69%), with the remaining patients diagnosed as migraine without aura (n= 19, 31%). Blurry vision was the most commonly reported aura symptom. Less frequently, the perception of flashing lights, bright coloured or back spots were stated as visual auras. Paraesthesia and numbness affecting the arms, legs and/or face were most commonly reported as a sensory aura. One patient also experienced a familiar smell as a sensory aura and one patient reported facial droop as a motor aura. Motor weakness affecting the upper and/or lower limbs was least frequently reported as a migraine aura.

The headache pain experienced by patients was typically unilateral and intermittent in nature. Some patients also suffered from less typical bilateral continuous headaches. As outlined in table 3.2.2, the mean headache duration for the overall study sample (n=60) was 7 hours, the shortest time being half an hour and the longest headache lasting up to 72 hours. Most patients had a family history of migraines, most frequently along the maternal side of the family. See table 3.2.1 for further information on migraine characteristics.

Migraine feature	N	% (of N = 60)
Nausea	41	69
Vomiting	32	53
Photophobia	50	83
Phonophobia	49	82
Presence of an aura	41	69
Visual aura	36	61
Sensory aura	22	37
Motor aura	8	14
Family history of migraine	44	74

Table 3.2.1- Information on the migraine-associated symptoms suffered and family history of migraine

Category	Headache Duration (hours)
Mean	7
Median	2
Mode	1
Minimum	0.5
Maximum	72
1st quartile	0.5
2nd quartile	2
3rd quartile	6
4th quartile	72

Table 3.2.2- Information on the duration of headaches suffered by the migraine study sample

Migraine variables

The PedMIDAS tool produced four main separate variables:

1. Total PedMIDAS scores used as a proxy for migraine severity
2. Four PedMIDAS migraine severity grades based on total PedMIDAS scores[186]:
    - Grade I (little to nothing): Total PedMIDAS score 0 to 10
    - Grade II (mild): Total PedMIDAS score 11 to 30
    - Grade III (moderate): Total PedMIDAS score 31 to 50
    - Grade IV (severe): Total PedMIDAS score greater than 50
3. Monthly headache frequency
4. Three monthly headache frequency groups[187]:
    - Group 1: Less than 4 monthly headaches
    - Group 2: 4- 10 monthly headaches
    - Group 3: Greater than 10 monthly headache

Distribution of PedMIDAS scores and monthly headache frequency values

As can be seen from table 3.2.3, the mean PedMIDAS score for the total 60 patients was 28.8 (s.d= 32.0), which fitted the profile of mild migraine severity (grade II). The minimum PedMIDAS score of zero which was reported by four patients in this pilot study, indicated these patients suffered from headaches that had no effect on their social, academic or domestic activities, as determined by the PedMIDAS tool. The maximum PedMIDAS score reported in this pilot study (PedMIDAS= 161) was scored by one patient, who also reported the maximum monthly headache frequency of 30 headaches a month. Two patients suffered from only 1 headache a month (the minimum reported monthly headache frequency); however these were not the same patients that scored the minimum PedMIDAS score of zero.

Distribution	Migraine severity (PedMIDAS score)	Monthly Headache Frequency
Mean	28.8	9
Median	21.0	8
Std. Deviation	32.0	6
Minimum	0.0	1
Maximum	161.0	30

Table 3.2.3- Distribution of PedMIDAS scores and monthly headache frequency

Category	Characteristic	Mean raw PedMIDAS scores (s.d)	Mean monthly headache Frequency (s.d)
Gender	*Female (n=34)*	30.2 (36.5)	8 (5)
	Male (n= 26)	26.8 (25.3)	10 (7)
Age	*6 to 12 years (n= 37)*	22.2 (21.4)	8 (6)
	13 to 16 years (n=23)	39.4 (42.4)	10 (7)
BMI status	*Normal weight (n=46)*	28.8 (34.5)	8 (6)
	Overweight (n=9)	30.7 (23.5)	11 (8)
	Obese (n=5)	25.4 (22.6)	9 (3)
Race	*Caucasian (n=58)*	28.2 (32.3)	9 (6)
	Mixed Race (n=2)	47.0 (15.6)	12 (6)

Table 3.2.4- Mean PedMIDAS scores and monthly headache frequency according to patient characteristics

As can be seen from table 3.2.3 the mean monthly headache frequency for the total study sample was 9 (s.d= 6) which fitted the category of 4 to 10 headaches a month (group 2). The median value for headache frequency was 8 monthly headaches. Only 6 patients (10%) met the criteria for a chronic daily headache diagnosis (≥15 monthly headaches), whilst the remaining majority of 54 children (90%) suffered from episodic migraine (≤15 monthly headaches).

The number of patients distributed among each migraine severity grade and headache frequency group were plotted on histograms that can be seen in figures, 3.2.1 and 3.2.2.

Figure 3.2.1 shows the frequency of patients in each migraine severity grade decreases as the severity grade increases. Figure 3.2.2 shows there are more patients that suffer 4 to 10 monthly headaches than in the other two headache frequency groups.

Figure 3.2.1
Distribution of patients according to the four migraine severity grades

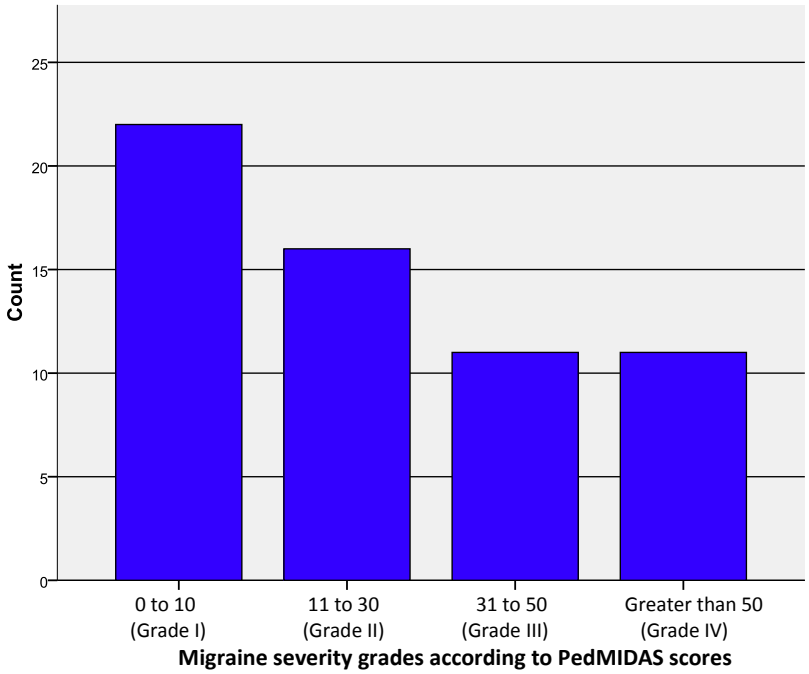
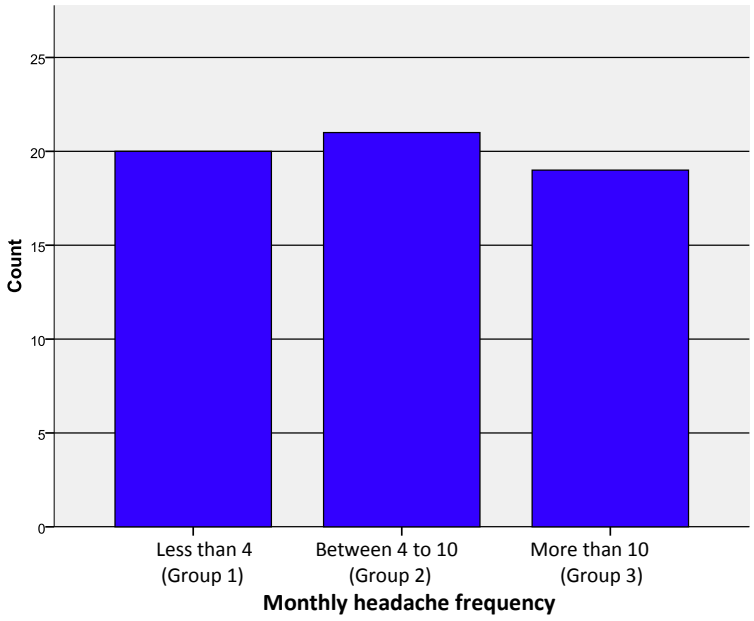


Figure 3.2.2
Distribution of patients according to the three monthly headache frequency groups



PedMIDAS scores and monthly headache frequency according to BMI status

As outlined in table 3.2.4, according to BMI status, the highest mean PedMIDAS score was found in the overweight category (PedMIDAS= 30.7) and the highest mean monthly headache frequency was also found in the overweight category (11 headaches per month). The lowest mean PedMIDAS score was found in the obese category (PedMIDAS= 25.4) and the lowest mean monthly headache value was found in the normal weight category (8 headaches per month). See table 3.2.4 for further details on PedMIDAS scores according to age, BMI status and gender.

Chapter 3.3

Body Mass Index Results

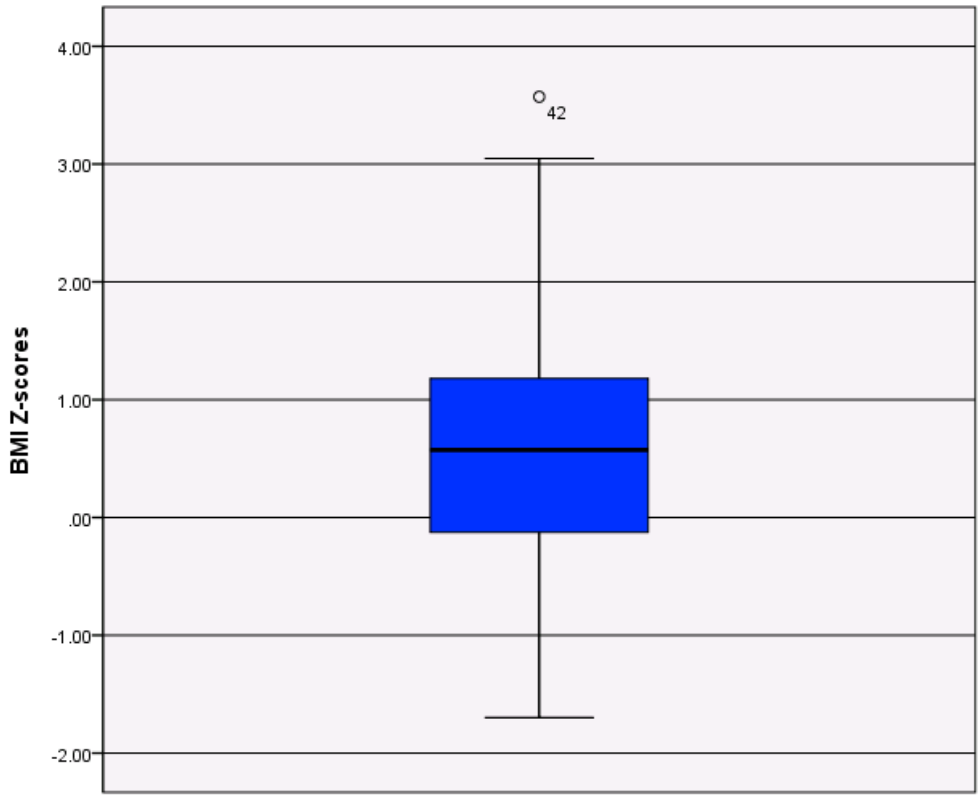
Distribution of BMI raw scores BMI z-scores

Body mass index z-scores were plotted as a histogram on figure 3.3.1, which shows a non-skewed distribution of BMI z-scores. The data for BMI z scores was of a parametric distribution. As can be seen from table 3.3.1, the mean BMI z-score of 0.62 for this study sample was closely related to the median value of 0.57.

Statistic	BMI Z-scores
Mean	0.62
Std. Deviation	1.14
Median	0.57
Skewness	0.50
Minimum	-1.70
Maximum	3.57

Table 3.3.1- Distribution of BMI z-scores

Figure 3.3.1
Distribution of BMI z-scores as a box plot



BMI z-score correlations with migraine severity and monthly headache frequency

The spearman's rank correlation coefficient between BMI z-scores and total PedMIDAS scores was r_s= 0.09 (p= 0.46). The spearman's rank correlation coefficient between BMI z-scores and monthly headache frequency was r_s= 0.21 (p= 0.10). Given that none of these correlations were significant at the probability level of 0.05, the hypothesis that "BMI z-scores will have a significantly (p≤ 0.05) positive correlation with PedMIDAS scores and monthly headache frequency", was rejected.

Distributions of BMI z-scores according to the migraine categories

BMI z-values were plotted as histograms according to the four grades of migraine severity and the three groups of monthly headache frequency. Figure 3.3.2 shows that the mean BMI z-score increased with every migraine severity grade up until grade III, but then decreased in grade IV. Figure 3.3.3 shows that the mean BMI z-score increased with every monthly headache frequency group.

Figure 3.3.2
Distribution of BMI z-scores according to the four migraine severity grades

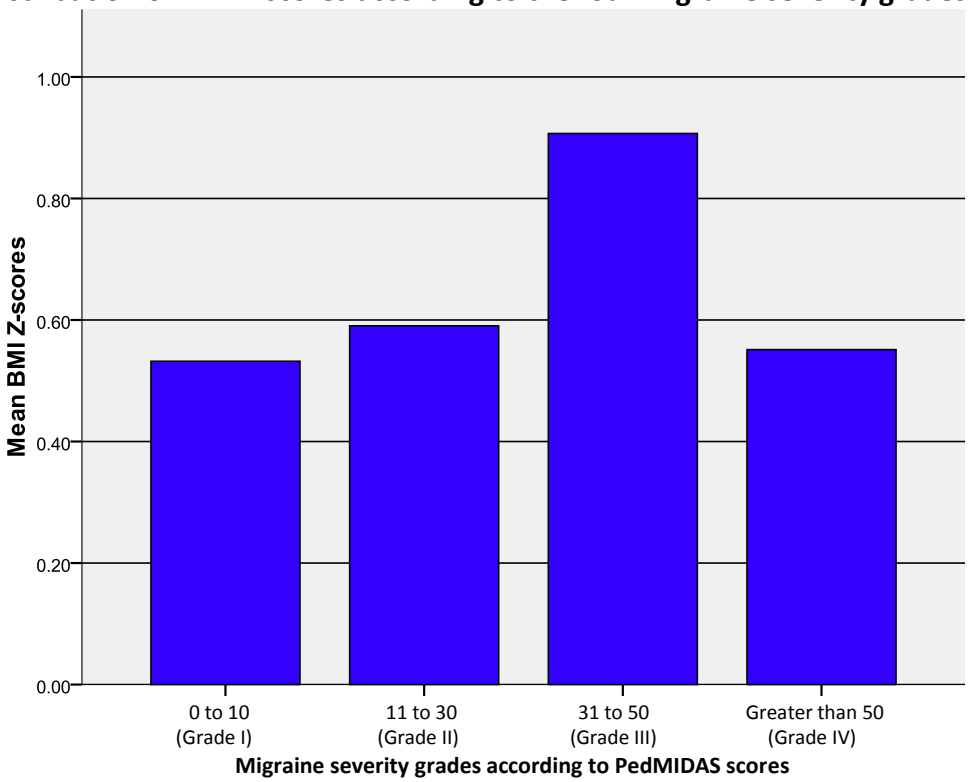
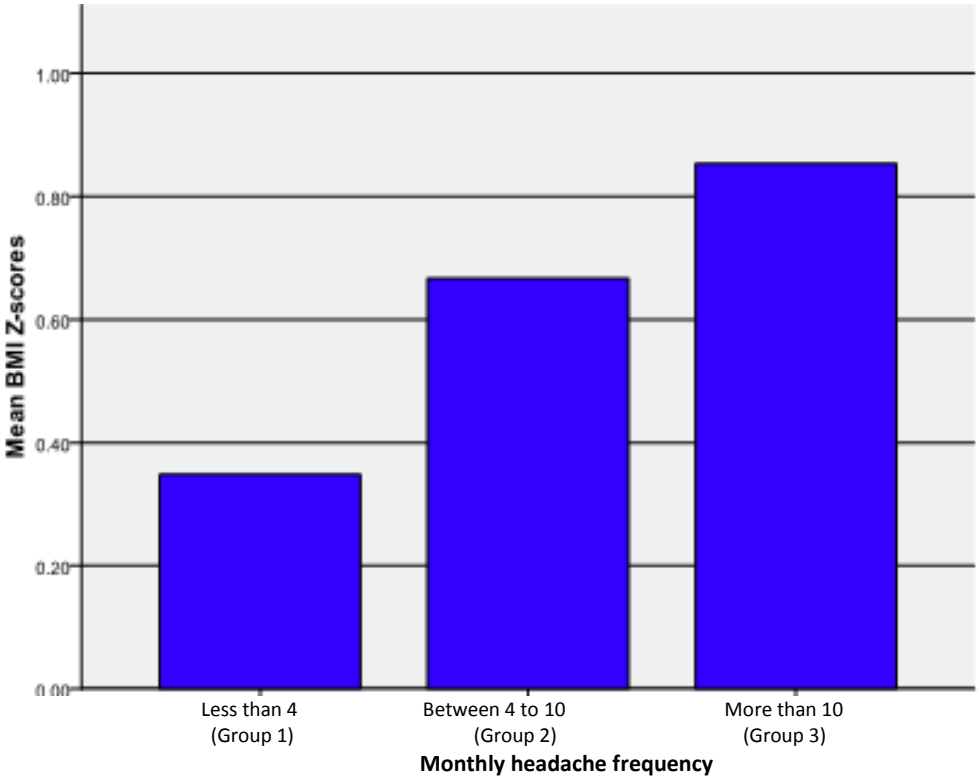


Figure 3.3.3
Distribution of BMI z-scores according to the three monthly headache frequency groups



Comparison of BMI z-scores between the migraine groups

As outlined in table 3.3.2, the F-value of 0.28 for the difference in BMI z-scores between the four migraine severity grades was insignificant at the corrected probability level of 0.025 (p=0.84). For this reason the hypothesis, “BMI z-scores will significantly differ between the four grades of migraine severity”, was rejected.

The F-value of 0.99 for the difference in BMI z-scores between the three headache frequency groups was insignificant at the corrected probability level of 0.025 (p=0.38). For this reason the hypothesis, “BMI z-scores will significantly differ between the three groups of headache frequency”, was rejected.

ANOVA test result	Grouping Variable: Four grades of PedMIDAS migraine severity	Grouping Variable: Three monthly headache frequency groups
F- value	0.28	0.99
p-value	0.84	0.38

Table 3.3.2- ANOVA test results for the comparison of BMI z-scores between the migraine groups

Chapter 3.4

Dutch Eating Behaviour Questionnaire (DEBQ) results

Of the 60 patients recruited, 23 children aged between 12 to 16 years completed the DEBQ (adolescent version) and 35 children aged between 7 to 12 years completed the DEBQ-C. Two children were unable to complete either tool because they were younger than 7 years. However as previously stated, the DEBQ (adolescent version) and DEBQ-C raw scores were converted to age and sex adjusted standardised DEBQ z scores.

Distribution of DEBQ z-scores

Statistical description	DEBQ- Em Z-score	DEBQ- Ext Z-score	DEBQ- Rest Z-score
Mean	0.08	-0.48	0.15
Median	-0.33	-0.53	0.04
Mode	-0.71	-0.49	-1.13
Minimum	-1.49	-3.31	-1.35
Maximum	5.29	2.29	3.03

Table 3.4.1- Distribution of DEBQ z-scores (Em= emotional eating, ext= external eating, rest= restrained eating)

Table 3.4.1, shows that the mean emotional eating z-score of 0.08 was very different to the mode (z-score= -0.71) and median (z-score= -0.33) emotional eating z-scores. For the external eating z-scores, the difference between the mean value -0.48, median value of -0.53 and mode value -0.49, was very small. With respect to restrained eating subscale, the mean z-score of 0.15 was very different to the mode z-score value of -1.13.

Figure 3.4.1 shows that the distribution of emotional eating z-scores was positively skewed. This is consistent with the fact that this data set was of a non-parametric distribution. Figure 3.4.2 illustrates how the external eating z-scores were normally distributed which supported the calculation that this dataset was of a parametric distribution. Figure 3.4.3 illustrates there was a positively skewed distribution of restrained eating z-scores. This supports the calculation that this data set was of a non-parametric distribution.

Figure 3.4.1
Box and whisker plot of DEBQ emotional eating z-scores

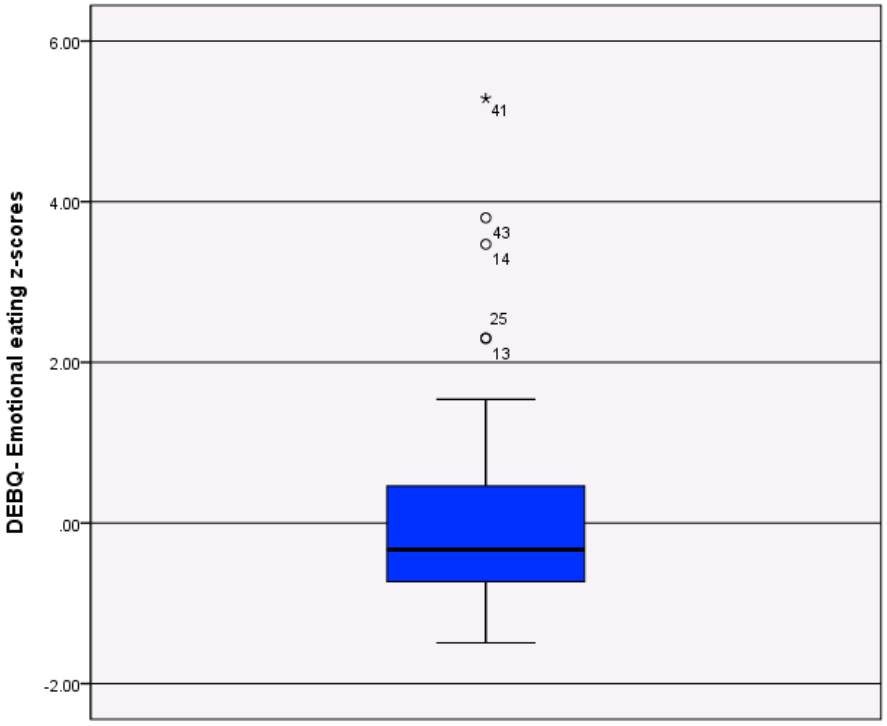


Figure 3.4.2
Box and whisker plot of DEBQ external eating z-scores

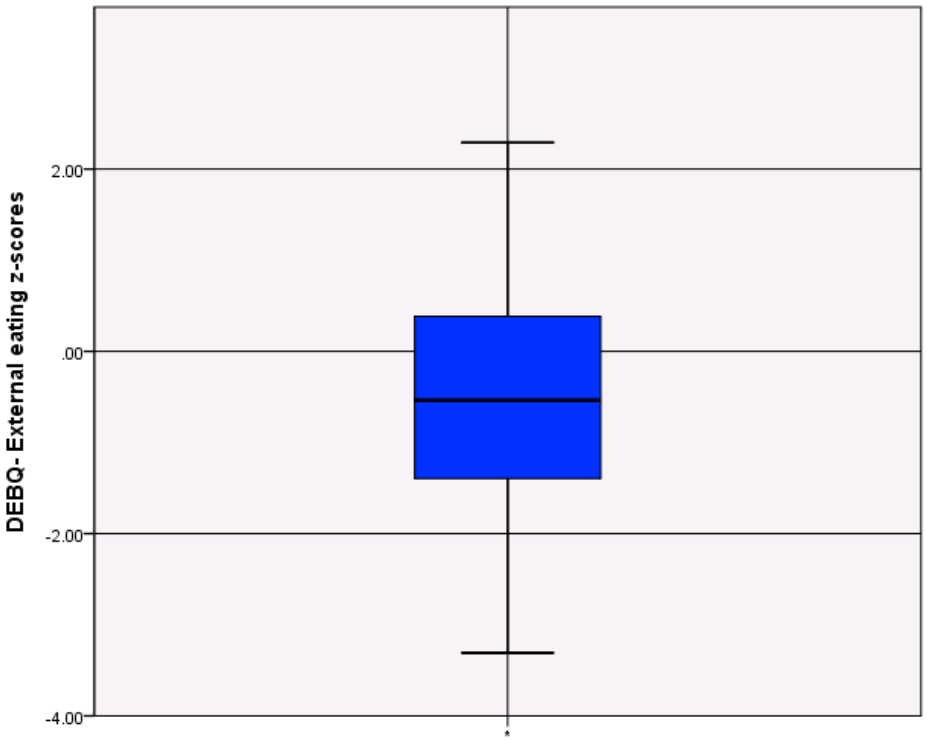
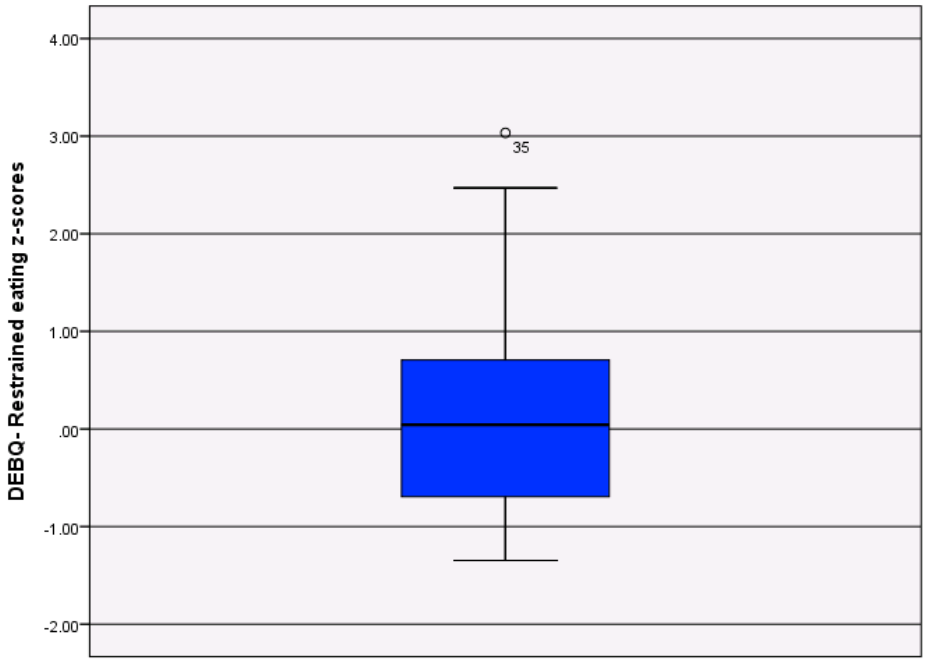


Figure 3.4.3
Box and whisker plot of DEBQ restrained eating z-scores



DEBQ/DEBQ-C raw scores according to mean reference range

As outlined in tables 3.4.2, the mean raw emotional eating score for children issued with the DEBQ (adolescent version) in females was 1.85 (s.d= 0.46) and 1.62 (s.d= 0.62) in males, both of which were within normal limits of the reference range values. The mean DEBQ (adolescent version) raw external eating score in boys at 2.3 (s.d= 0.67) was below the reference mean. The mean DEBQ (adolescent version) external eating raw score of 2.36 (s.d= 0.43) in girls was within normal limits. The mean DEBQ (adolescent version) restrained eating scores, 1.62 (s.d= 0.6) for males and 2.38 (s.d= 0.99) for females, were both within normal ranges.

As can be seen in table 3.4.3 the mean DEBQ-C raw scores for emotional, external and restrained eating for boys and girls were all greater than the average reference ranges (the average reference ranges can be seen in table 3.4.4). This indicates a high level of each type of eating behaviour was present among children aged 7 to 12 years in this pilot study.

DEBQ for adolescents subscale	Mean raw score for girls	Mean raw score for boys
DEBQ- Emotional eating	1.85 (0.46)	1.62 (0.60)
DEBQ- External eating	2.36 (0.43)	2.30 (0.67)
DEBQ- Restrained eating	2.38 (0.99)	1.62 (0.60)

Table 3.4.2- Mean DEBQ (adolescent version) raw scores for girls and boys separately

DEBQ-C subscale	Mean raw score for girls	Mean raw score for boys
DEBQ (children)- Emotional eating	1.53 (0.63)	1.42 (0.48)
DEBQ (children)- External eating	2.04 (0.70)	2.06 (0.51)
DEBQ (children)- Restrained eating	1.66 (0.58)	1.62 (0.49)

Table 3.4.3- Mean DEBQ-C raw scores for girls and boys separately

DEBQ Subscale	Female reference value range	Male reference value range
DEBQ (adolescent version)- Emotional eating	1.69-2.13	1.24-2.84
DEBQ (adolescent version)- External eating	2.57-3.57	2.19-4.31
DEBQ (adolescent version)- Restrained eating	1.85-2.55	0.92-2.12
DEBQ-C (child version)- Emotional eating	1.24	1.27
DEBQ-C (child version)- External eating	2.00	1.90
DEBQ-C (child version)- Restrained eating	1.64	1.53

Table 3.4.4- Reference value ranges outlined for each of the DEBQ and DEBQ-C subscales

Emotional, external and restrained eating scores for each of the 58 DEBQ questionnaires composed of both the adolescent and child versions were categorised according to whether they were below, above or within normal reference ranges. The reference ranges were calculated by the same studies from which the z-scores were calculated and are outlined in chapter 2.3 of this thesis (section on the DEBQ tool) and the values are listed in table 3.4.4[73,165]. As outlined in table 3.4.5, there was a high number of children with raw external eating scores below (n= 30, 52%) and above (n=23, 40%) the normal reference mean range. Only 5 (8%) patients had an external eating score within the normal reference range. This indicated a large proportion of children in this pilot study had very low and very high external eating levels. With respect to restrained eating, only 14 patients had a raw score within the normal reference range, which again indicated many of the patients had very high (n= 22) and very low (n= 22) restrained eating levels. There were fewer patients with raw emotional eating scores outside of the normal reference range.

DEBQ/DEBQ-C Subscale	No. of patients with a raw score < reference mean (% of N=58)	No. of patients with a raw score within reference range (% of N= 58)	No. of patients with a raw score > reference mean (% of N= 58)
Emotional	22 (38)	18 (31)	18 (31)
External	30 (52)	5 (8)	23 (40)
Restrained	22 (38)	14 (24)	22 (38)

Table 3.4.5- The population of patients with DEBQ and DEBQ-C scores below, within or above the normal reference range DEBQ/DEBQ-C values

Correlations between DEBQ subscale z-scores and PedMIDAS scores

As can be seen from table 3.4.6, there were no significant correlations ($p \leq 0.05$) between any of the DEBQ subscale z-scores and PedMIDAS raw scores. Based on this finding the hypothesis, "emotional, external and restrained eating z-scores of the DEBQ will have a significantly ($p \leq 0.05$) positive correlation with PedMIDAS (migraine) severity scores" was rejected.

DEBQ Subscale	PedMIDAS r_s (p-value)	Monthly Headache Frequency r_s (p-value)
Emotional eating z-scores	0.19 (0.14)	0.07 (0.59)
External eating z-scores	-0.07 (0.63)	-0.01 (0.90)
Restrained eating z-scores	0.05 (0.72)	0.3 (0.83)

Table 3.4.6- Spearman rank correlation results between DEBQ subscale z-scores and PeMIDAS scores/monthly headache frequency

Correlations between DEBQ subscale z-scores and monthly headache frequency

As can be seen from table 3.4.6, there were no significant correlations between any of the DEBQ subscale z-scores and monthly headache frequency. Based on this finding the hypothesis, "emotional, external and restrained eating z-scores of the DEBQ will have a significantly ($p \leq 0.05$) positive correlation with monthly headache frequency" was rejected.

Distribution of DEBQ z-scores according to migraine severity/ headache frequency groups

Mean DEBQ subscale z-scores were plotted as histograms according to the four PedMIDAS migraine severity grades and the three monthly headache frequency groups. These are shown in figures 3.4.4 to 3.4.9. Figure 3.4.4 shows the highest mean emotional eating z-scores were in migraines grades II (11-30 PedMIDAS scores, mean= 0.54) and III (31-50 PedMIDAS scores, mean= 0.42). Figures 3.4.5 and 3.4.6 show the highest mean external eating z-score (mean= -0.19) and restrained eating z-score (mean= 0.56) were each in migraine severity grade III. As illustrated in figures 3.4.7 to 3.4.9, the lowest headache frequency group (< 4 monthly headaches) had the highest mean emotional eating (mean= 0.5), external eating (mean= -0.2) and restrained eating (0.26) z-scores.

Figure 3.4.4
Histogram of mean emotional eating z-scores plotted according to the four migraine severity grades

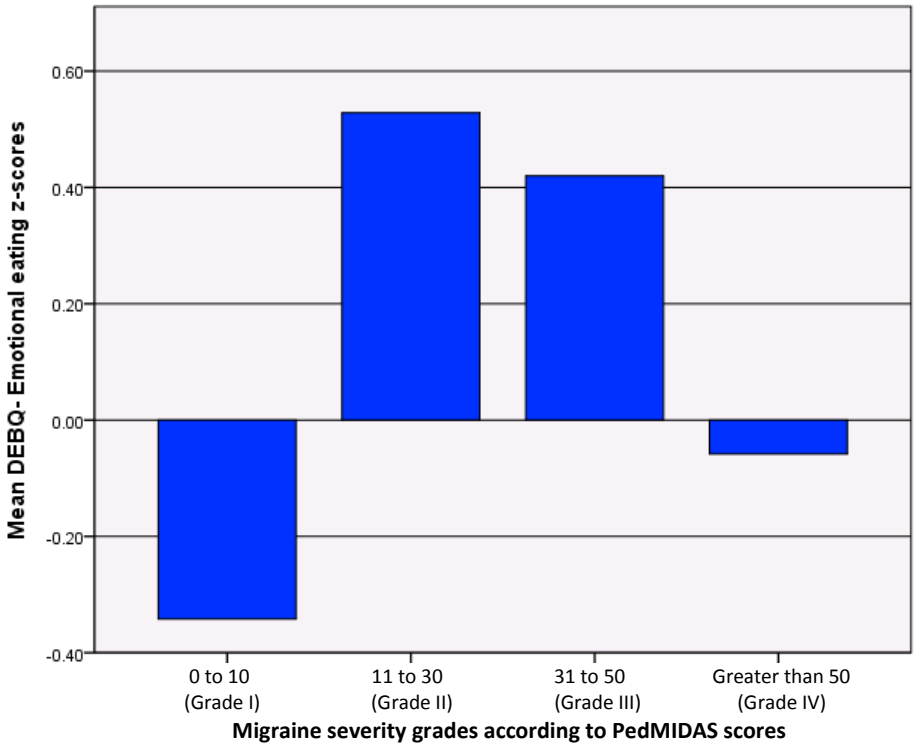


Figure 3.4.5
Histogram of mean external eating z-scores plotted according to the four migraine severity grades

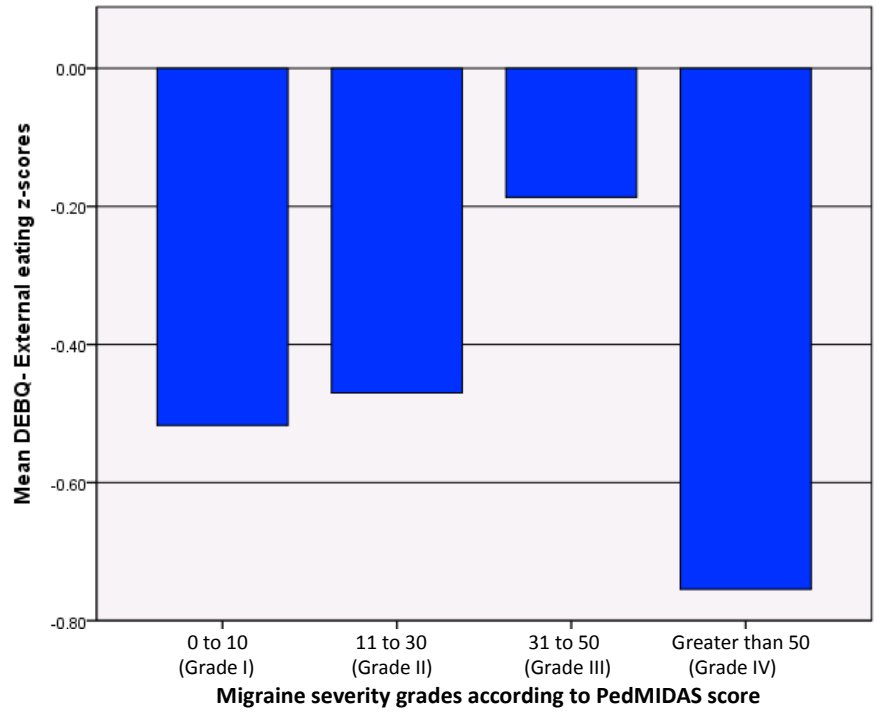


Figure 3.4.6
Histogram of mean restrained eating z-scores plotted according to the four migraine severity grades

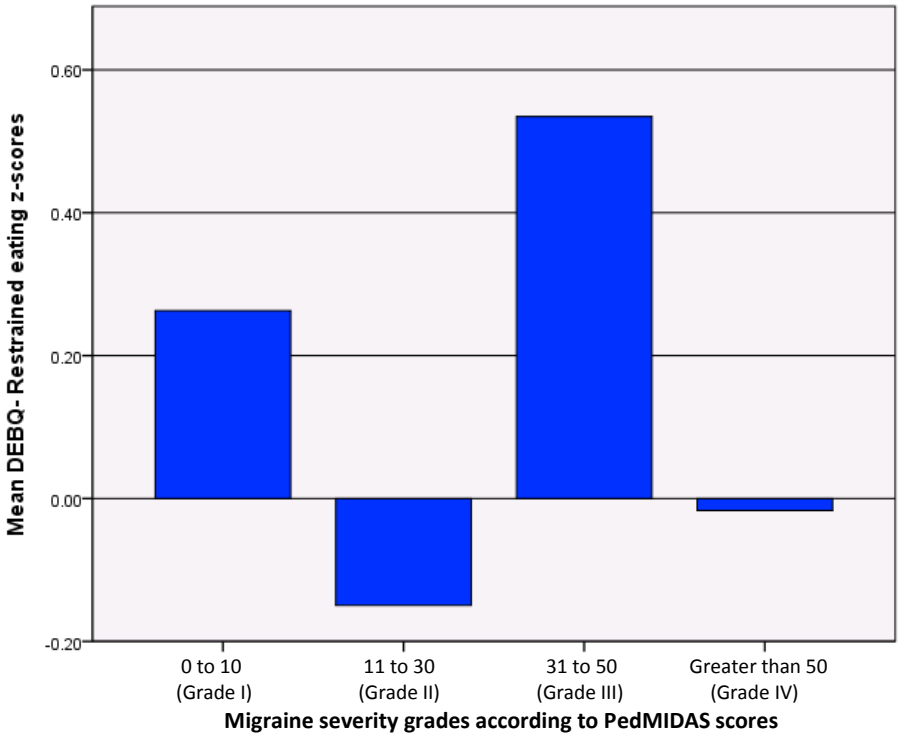


Figure 3.4.7
Histogram of mean emotional eating z-scores plotted according to the three monthly headache frequency groups

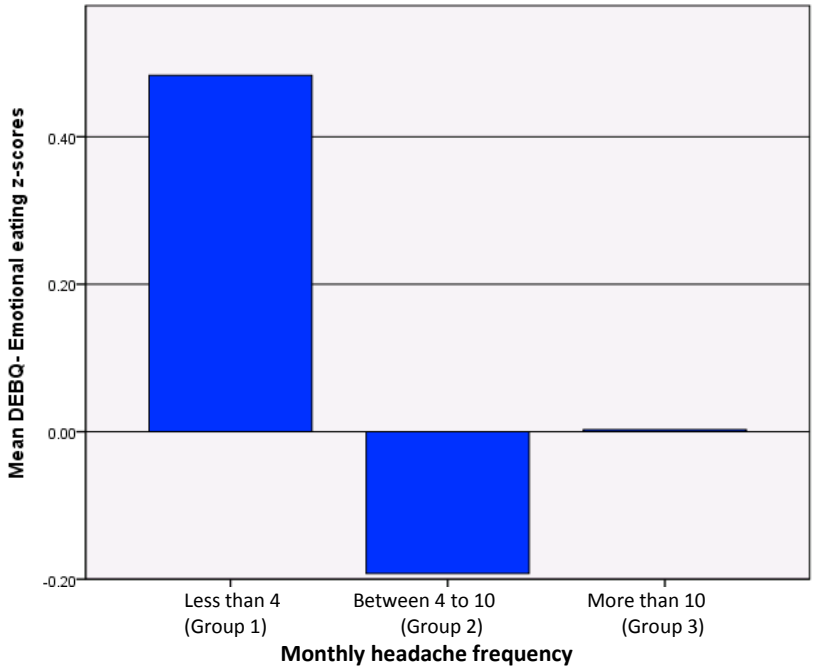


Figure 3.4.8
Histogram of mean external eating z-scores plotted according to the three monthly headache frequency groups

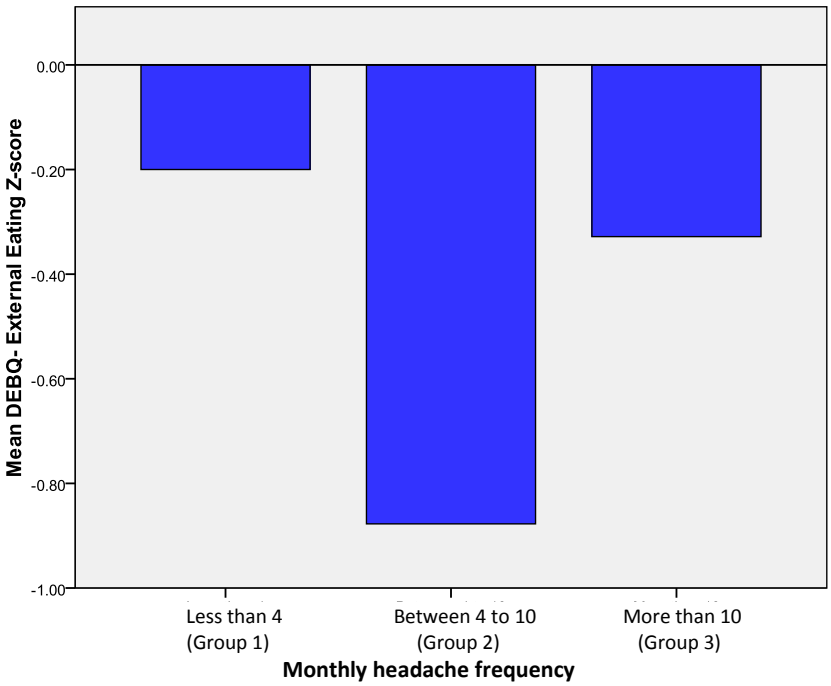
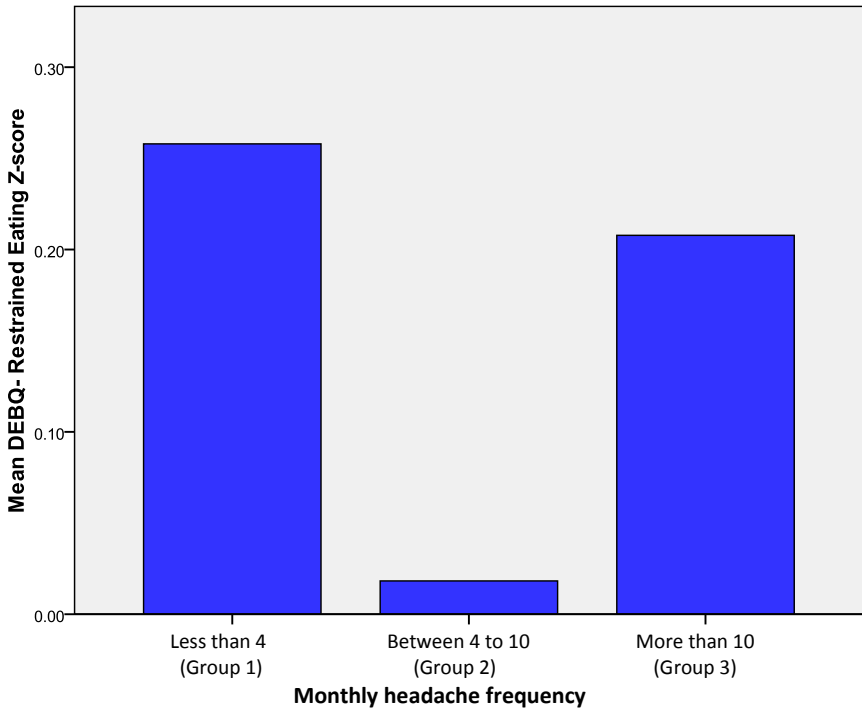


Figure 3.4.9
Histogram of mean restrained eating z-scores plotted according to the three monthly headache frequency groups



Comparison of DEBQ subscale z-scores between the four migraine severity grades

As can be seen from table 3.4.7, the chi squared values for emotional, external and restrained eating z-scores were insignificant at the corrected probability level of 0.008. For this reason, the hypothesis "emotional eating, external eating and restrained eating z-scores will significantly (p≤ 0.008) differ between the four grades of migraine severity (I, II, II, IV)", was rejected.

Kruskal-Wallis test result: PedMIDAS migraine severity groups	DEBQ- Emotional eating z-scores	DEBQ- External eating z-scores	DEBQ- Restrained eating z-scores
Chi-square	3.86	0.98	1.98
p-value	0.28	0.81	0.58

Table 3.4.7- Kruskal-Wallis test results for the comparison of emotional, restrained and external eating z-scores between the four PedMIDAS migraine severity grades

Comparison of DEBQ subscale z-scores between the three headache frequency groups

As can be seen from table 3.4.8, the chi squared values for emotional, external and restrained eating z-scores were all insignificant at the corrected probability level of 0.008. For this reason the hypothesis, "emotional eating, external eating and restrained eating z-scores will significantly (p≤ 0.008) differ between 3 groups of monthly headache frequency", was rejected.

Kruskall- Wallis test result: Monthly Headache Frequency categories	**DEBQ- Emotional eating z-scores**	**DEBQ- External eating z-scores**	**DEBQ- Restrained eating z-scores**
Chi-square	1.07	2.71	1.09
p-value	0.59	0.26	0.58

Table 3.4.8- Kruskal-Wallis test results for the comparison of emotional, restrained and external eating z-scores between the three headache frequency groups

DEBQ z-score correlations with Child Behaviour Checklist (CBCL) T-scores

As outlined by table 3.4.9, at the probability level of 0.05, none of DEBQ subscale z-scores were significantly correlated with any of the CBCL subscale T-scores. For this reason the hypothesis, "CBCL subscale T-scores will have a significantly (p≤ 0.05) positive correlation with emotional, external and restrained eating z-scores of the DEBQ" was rejected.

DEBQ Subscale	**CBCL Externalised Behaviours T-scores r_s (p- value)**	**CBCL Internalised Behaviours T-scores r_s (p- value)**	**CBCL Total T-scores r_s (p- value)**
Emotional Eating z-scores	-0.06 (0.65)	0.19 (0.16)	0.05 (0.73)
External eating z-scores	0.01 (0.95)	0.15 (0.27)	0.01 (0.94)
Restrained eating z-scores	-0.12 (0.36)	-0.08 (0.55)	-0.09 (0.49)

Table 3.4.9- Spearman rank test results for the correlations between DEBQ subscale z-scores and CBCL subscale T-scores

Chapter 3.5

Child Eating Behaviour Questionnaire (CEBQ) results

A total of 37 patients fitted the age criteria (5-12 years) for the CEBQ, of these 19 were female and 20 were male. As outlined in table 3.5.1, the mean CEBQ z-scores for the enjoyment of food (mean= -0.12, median= -0.11), desire to drink (mean= -0.13, median= -0.19) and food fussiness (mean= -0.09, median= -0.07) were very similar to their respective median scores.

CEBQ subscale	Mean (s.d)	Median	Minimum	Maximum
Food responsiveness (FR)	-0.26 (0.95)	-0.38	-1.63	1.75
Emotional over eating(EOE)	-0.14 (1.09)	-0.50	-1.33	2.83
Enjoyment of food (EF)	-0.12 (1.14)	-0.11	-2.94	1.75
Desire to drink (DD)	-0.13 (0.97)	-0.19	-1.73	1.75
Satiety responsiveness (SR)	-0.23 (1.12)	-0.43	-2.43	1.86
Slowness of eating (SE)	-0.70 (1.23)	-0.86	-3.00	1.64
Emotional under eating (EUE)	-0.99 (1.27)	-0.86	-3.00	1.79
Food fussiness (FF)	-0.09 (1.21)	-0.07	-2.33	2.33

Table 3.5.1- Distribution of CEBQ subscale z-scores

As outlined in table 3.5.2, the mean z-score for every CEBQ subscale was lower among females except for the food fussiness subscale, which had a higher mean z-score of 0.04 among females compared with a mean z-score of -0.21 among males. As outlined in table 3.5.2, the mean CEBQ z-scores were higher among the group of children aged 13 to 16 years for the FR, EF, DD and FF subscales, compared with children aged 5 to 12 years. Whilst children in the 5 to 12 year age group had higher mean CEBQ z-scores for the EOE, SR, SE and EUE subscales, compared with the 13 to 16 year age group.

Category	Characteristic	FR Mean (s.d)	EOE Mean (s.d)	EF Mean (s.d)	DD Mean (s.d)	SR Mean (s.d)	SE Mean (s.d)	EUE Mean (s.d)	FF Mean (s.d)
Gender	*Female*	-0.3 (1.05)	-0.26 (1.17)	-0.12 (1.08)	-0.36 (0.93)	-0.47 (0.90)	-1.01 (1.24)	-1.17 (1.44)	0.04 (1.04)
	Male	-0.23 (0.86)	-0.02 (1.02)	-0.11 (0.97)	-0.11 (1.30)	-0.11 (1.30)	-0.41 (1.17)	-0.83 (1.08)	-0.21 (1.37)
Age	*5-12 yrs*	-0.34 (0.93)	-0.08 (1.14)	-0.17 (1.14)	-0.20 (0.94)	-0.16 (1.11)	-0.54 (1.21)	-0.91 (1.13)	-0.22 (1.21)
	13-16 yrs	0.28 (0.96)	-0.50 (0.66)	0.26 (1.19)	0.37 (1.13)	-1.14 (0.93)	-1.78 (0.75)	-1.54 (2.04)	0.80 (0.85)

Table 3.5.2- Mean CEBQ subscale z-scores according to gender and age

Distribution of CEBQ subscale z-scores

The standardised z-score data for food responsiveness (FR), enjoyment of food (EF), desire to drink (DD), satiety responsiveness (SR), slowness of eating (SE), emotional under eating and food fussiness (FF) subscales all followed a parametric distribution. Emotional overeating (EOE) was the only CEBQ subscale with data of a non-parametric distribution.

Box and whisker plots were used to plot z-scores for each CEBQ subscale. Box and whisker plots for food responsiveness (fig- 3.5.1), emotional over-eating (fig- 3.5.2), desire to drink (fig- 3.5.4) and emotional under-eating (fig- 3.5.7) subscales are all positively skewed. The box and whisker plot for the enjoyment of food (fig- 3.5.3) subscale is negatively skewed. Figures 3.5.5 (satiety responsiveness), 3.5.6 (slowness of eating) and 3.5.8 (food fussiness) do not appear to be skewed.

Figure 3.5.1- Box plot of the food responsiveness (FR) z-scores

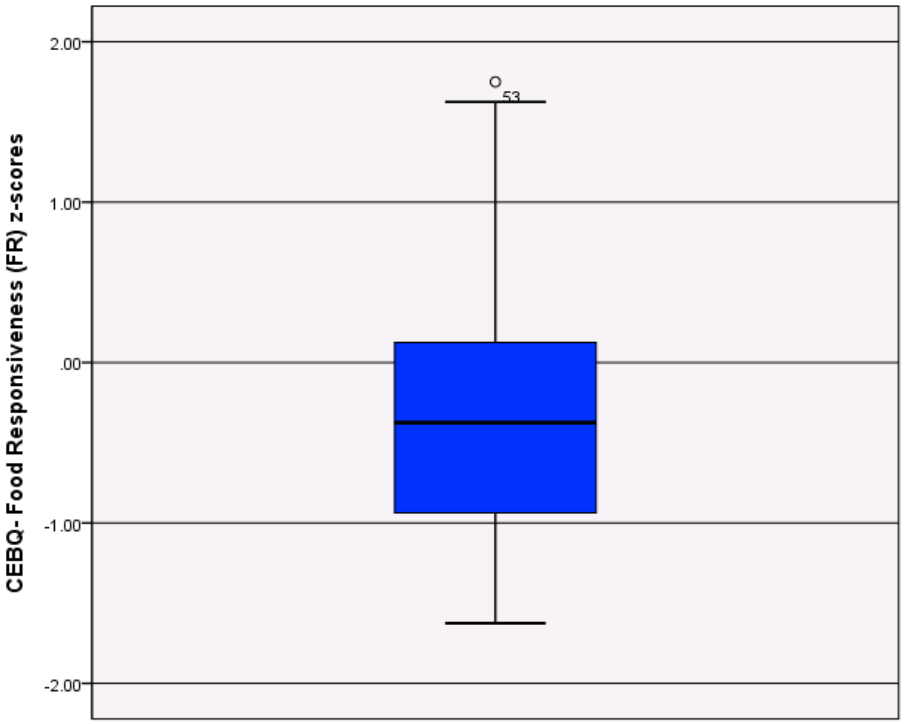


Figure 3.5.2- Box plot of the emotional over-eating (EOE) z-scores

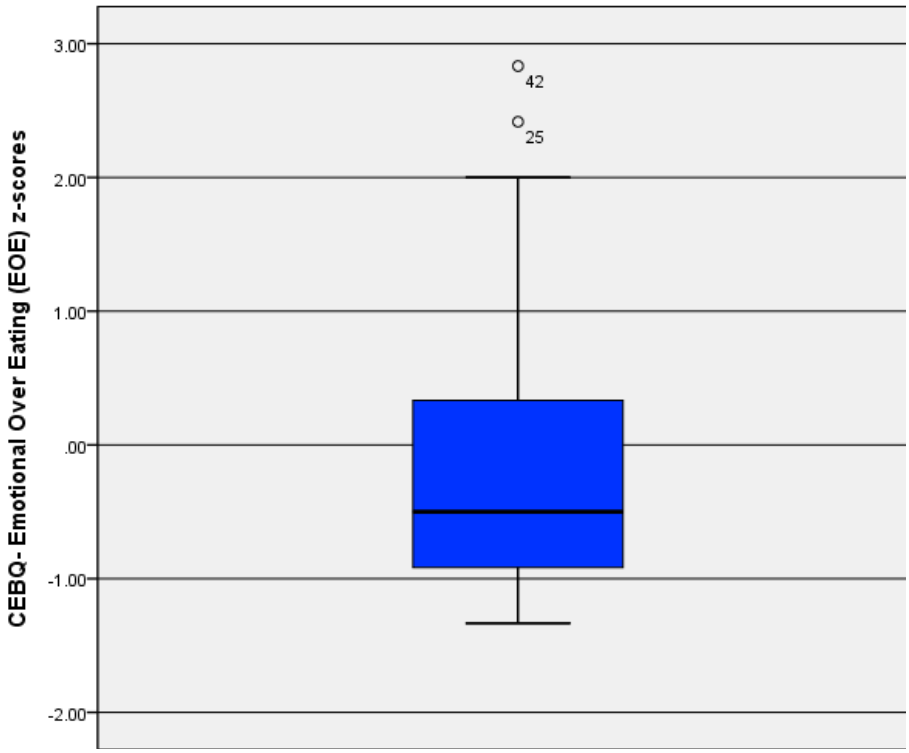


Figure 3.5.3- Box plot of the enjoyment of food (EF) z-scores

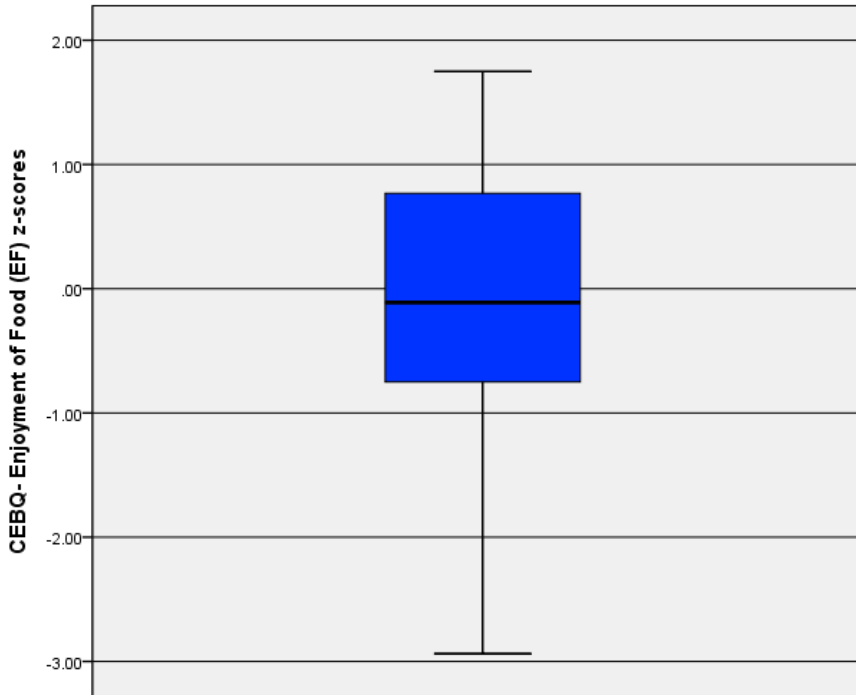


Figure 3.5.4- Box plot of the desire to drink (DD) z-scores

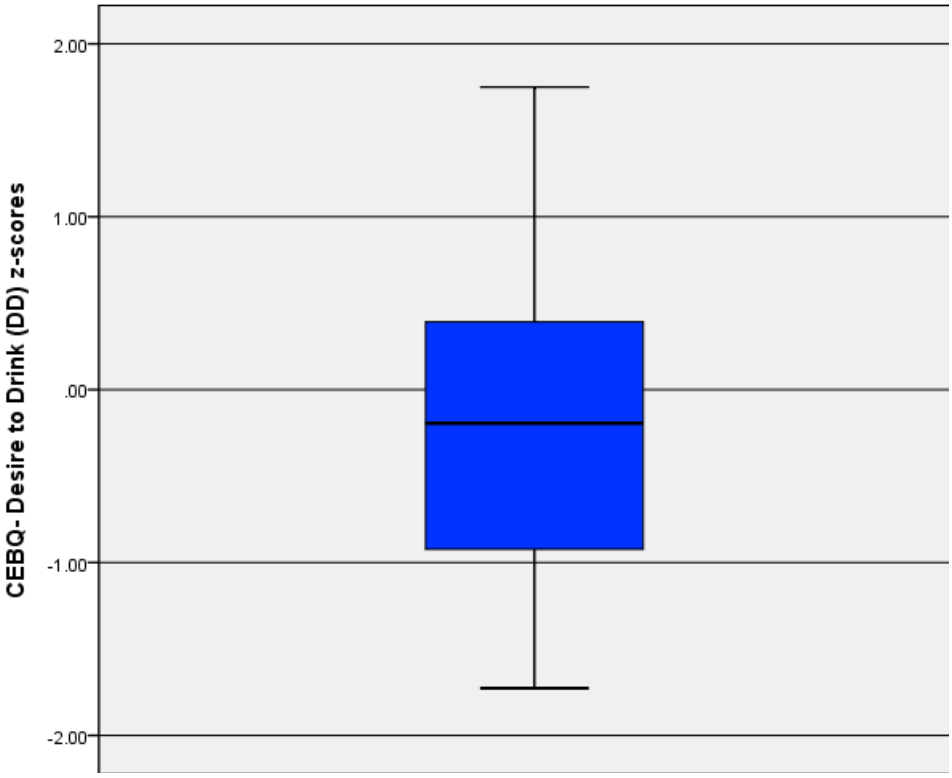


Figure 3.5.5- Box plot of the satiety responsiveness (SR) z-scores

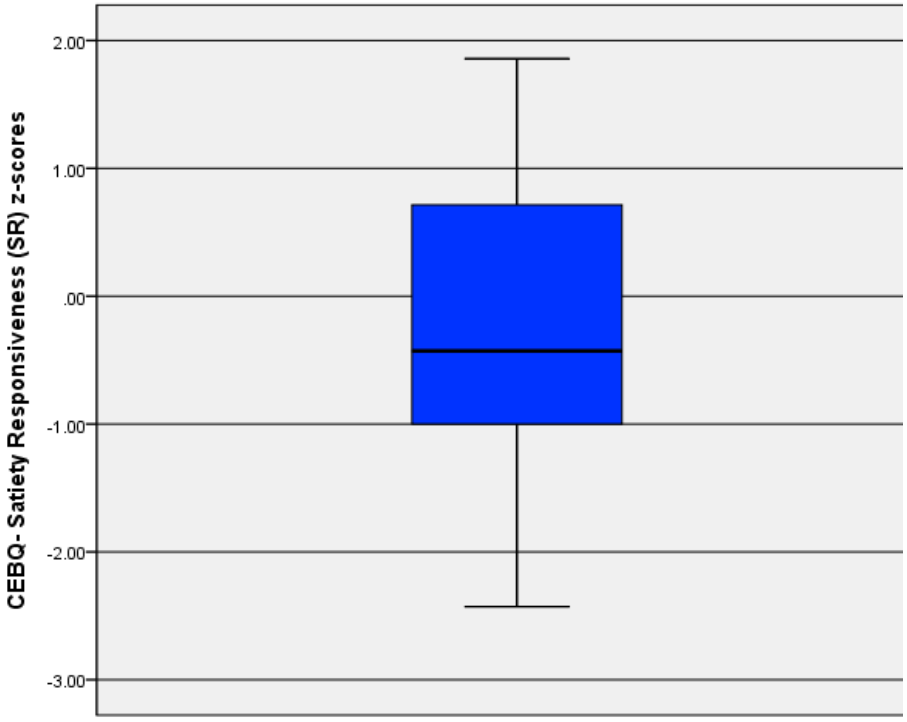


Figure 3.5.6- Box plot of the slowness of eating (SE) z-scores

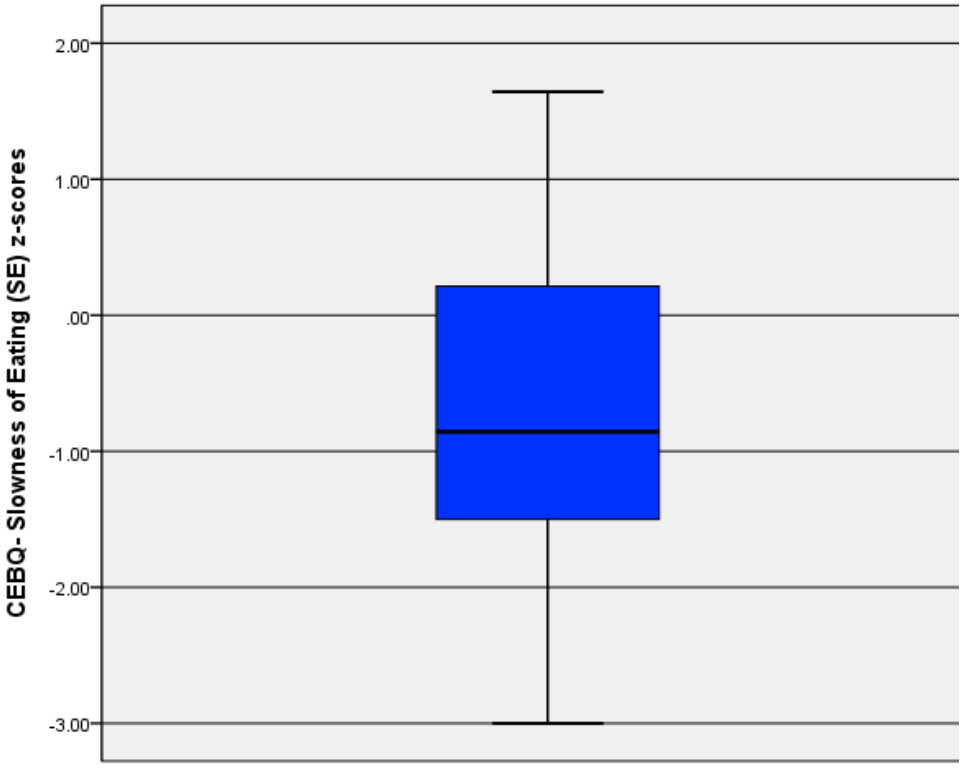


Figure 3.5.7- Box plot of the emotional under-eating (EUE) z-scores

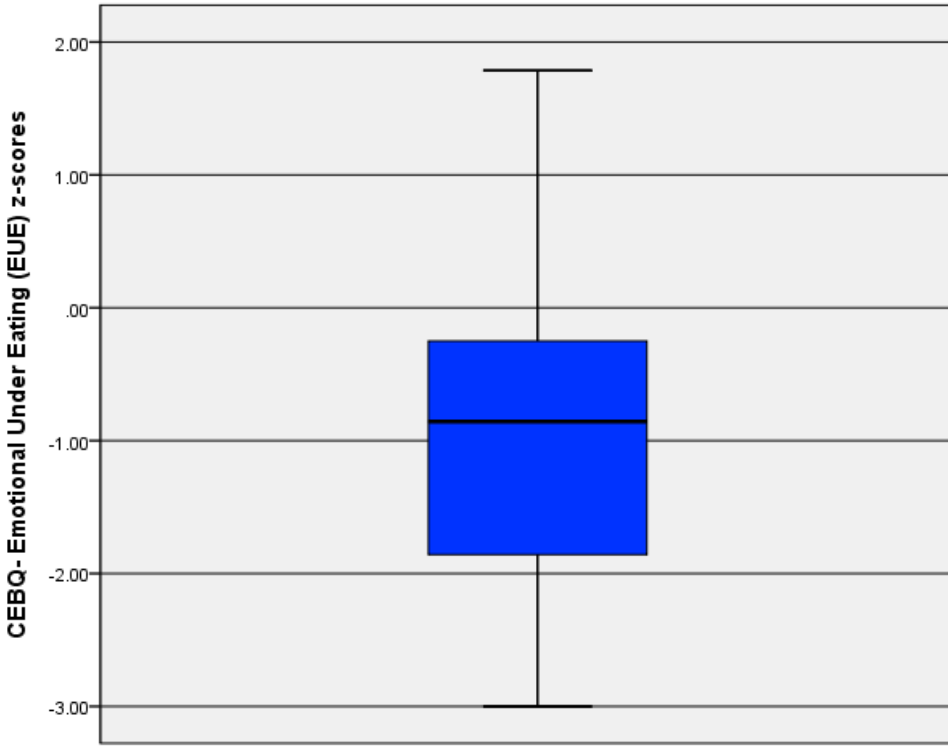
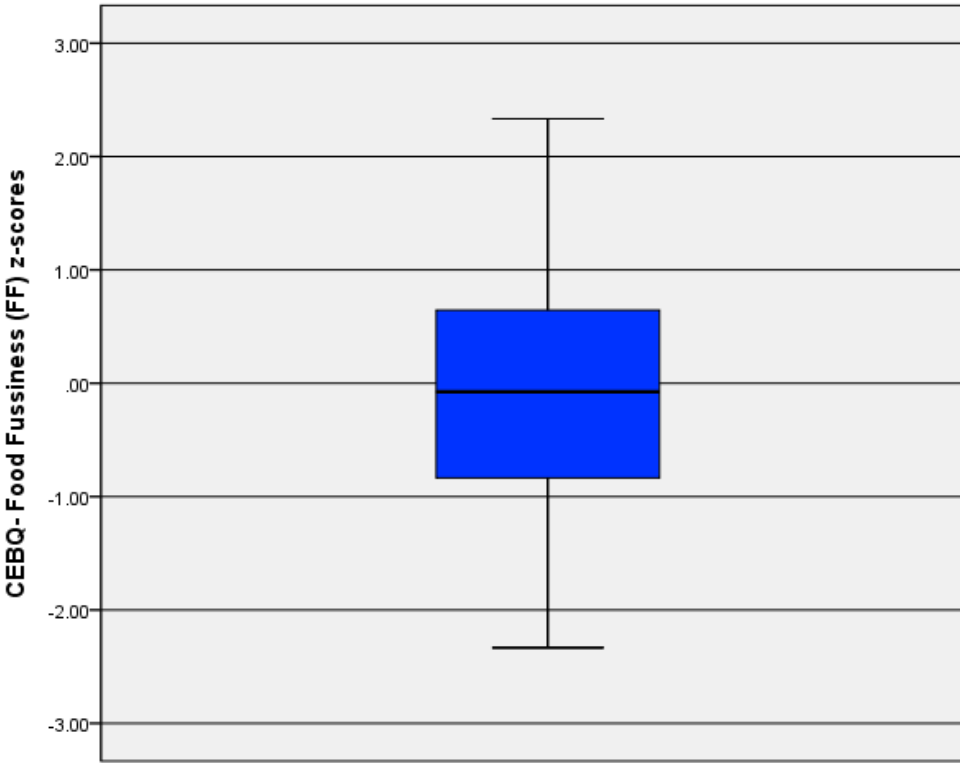


Figure 3.5.8- Box plot of the food fussiness (FF) z-scores



Frequency of patients with CEBQ subscale raw scores below/above the reference mean

The number of girls and boys with a raw score above or below the reference mean were calculated for each CEBQ subscale as can be seen from tables 3.5.3 and 3.5.4. The mean CEBQ raw score reference values are listed in table 3.5.5. Girls had a high proportion of raw scores below the reference mean for food responsiveness (n= 13; 68%), emotional overeating (n= 14; 74%), desire to drink (n=14; 74%), satiety responsiveness (n= 15, 79%), slowness of eating (n= 14; 74%) and emotional under-eating (n= 16; 84%).

CEBQ subscale: Girls	No. of patients with a raw CEBQ score below reference mean (% of N= 19)	No. of patients with a raw CEBQ score above reference mean (% of N= 19)
Food responsiveness (FR)	13 (68)	6 (32)
Emotional over eating(EOE)	14 (74)	5 (26)
Enjoyment of food (EF)	8 (42)	11 (59)
Desire to drink (DD)	14 (74)	5 (26)
Satiety responsiveness (SR)	15 (79)	4 (21)
Slowness of eating (SE)	14 (74)	5 (26)
Emotional under eating (EUE)	16 (84)	3 (16)
Food fussiness (FF)	9 (47)	10 (53)

Table 3.5.3- Number of girls with CEBQ subscales scores below/above reference mean

CEBQ subscale: Boys	No. of patients with a raw CEBQ score below reference mean (% of N= 18)	No. of patients with a raw CEBQ score above reference mean (% of N= 18)
Food responsiveness (FR)	14 (80)	4 (20)
Emotional over eating(EOE)	12 (65)	6 (35)
Enjoyment of food (EF)	11 (60)	7 (40)
Desire to drink (DD)	7 (40)	11 (60)
Satiety responsiveness (SR)	9 (50)	9 (50)
Slowness of eating (SE)	11 (60)	7 (40)
Emotional under eating (EUE)	14 (80)	4 (20)
Food fussiness (FF)	10 (55)	8 (45)

Table 3.5.4- Number of boys with CEBQ subscale scores below/above reference mean

Boys had a large proportion of raw scores below the reference mean for food responsiveness (n= 14; 80%) and emotional under-eating (n= 14; 80%). Boys also had an equal number of raw scores above and below the reference mean for the satiety responsiveness subscale. There were 7 more boys than girls (60% versus 26%, respectively) with a desire to drink raw score above the reference mean. There were 6 more boys than girls with a satiety responsiveness score above the reference mean (50% versus 21%, respectively).

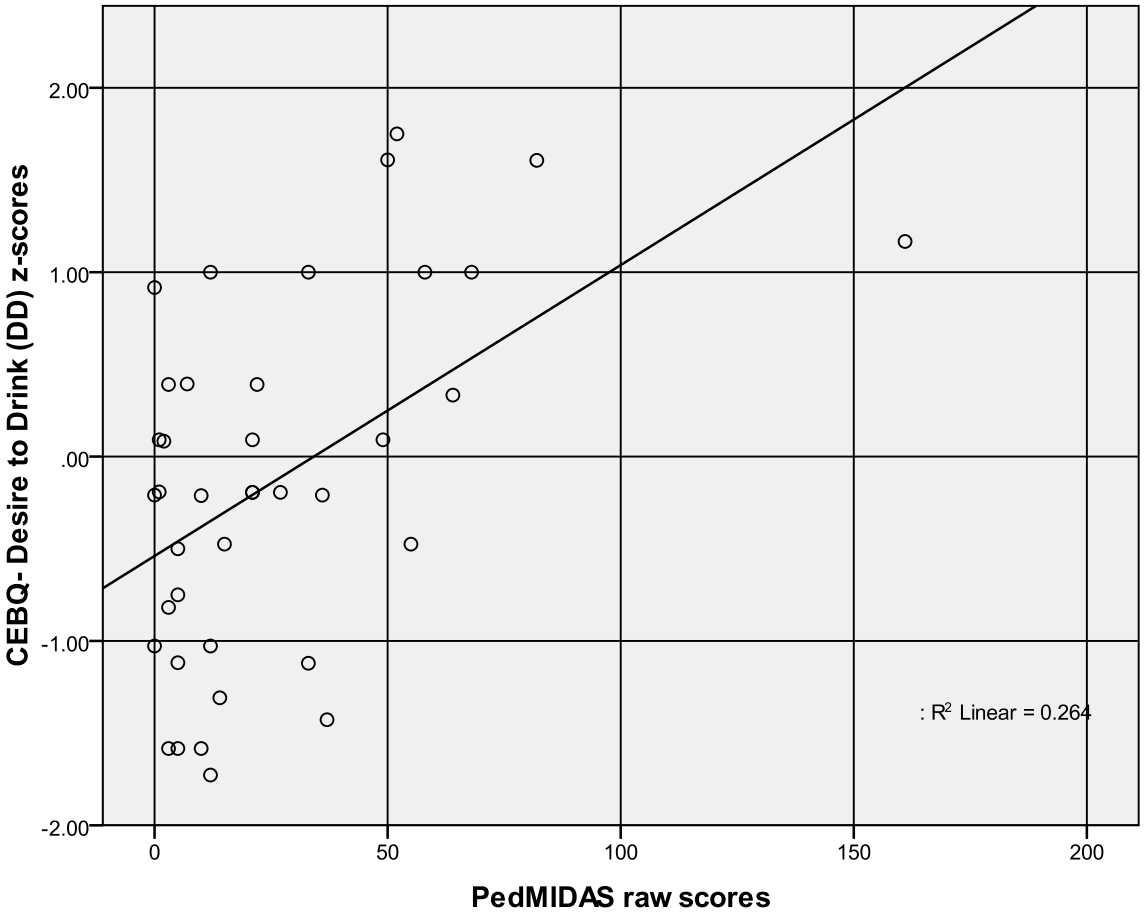
CEBQ subscale	Normal reference value in males	Normal reference value in females
Food responsiveness (FR)	2.3	2.2
Emotional over eating(EOE)	1.8	1.8
Enjoyment of food (EF)	3.6	3.6
Desire to drink (DD)	2.9	2.9
Satiety responsiveness (SR)	3.1	3.1
Slowness of eating (SE)	3.0	3.1
Emotional under eating (EUE)	3.1	3.0
Food fussiness (FF)	3.1	2.9

Table 3.5.5- Reference normal raw score values for each CEBQ subscale

Correlation between CEBQ subscale z-scores and PedMIDAS scores

As outlined in table 3.5.6, at the probability level of 0.05, the CEBQ desire to drink z-scores had a weak but significantly positive correlation with the PedMIDAS scores (r_s= 0.41, p= 0.01). Based on this finding the hypothesis that "the desire to drink (DD) z-scores of the CEBQ will have a significantly ($p \leq 0.05$) positive correlation with PedMIDAS severity scores", was accepted. On advice from the statistician involved in this pilot study, a correlation coefficient equal to or greater than 0.7 was considered a strong correlation. Given that the correlation coefficient (r_s) was 0.41 the correlation between the desire to drink subscale and PedMIDAS scores was considered to be quite weak. This point is further demonstrated in figure 3.5.9 by the weak association of dots in the scatter graph of PedMIDAS scores plotted against the CEBQ desire to drink (DD) z-scores.

Figure 3.5.9
Scatter graph of PedMIDAS scores plotted against CEBQ desire to drink (DD) z-scores



As can be seen in table 3.5.6, at the probability level of 0.05 the remaining CEBQ subscales were not significantly correlated with the PedMIDAS scores. For this reason the hypothesis of "standardised z-scores for food responsiveness (FR), emotional overeating (EOE) and enjoyment of food (EF) subscales of the CEBQ will have a significantly ($p \leq 0.05$) positive correlation with PedMIDAS scores" was rejected. The hypothesis of "standardised z-scores for satiety responsiveness (SR), slowness of eating (SE), emotional under eating (EUE) and food fussiness (FF) subscales of the CEBQ will have a significantly ($p \leq 0.05$) negative correlation with PedMIDAS scores" was also rejected.

Correlation between CEBQ z-scores and monthly headache frequency

As can be seen in table 3.5.6, none of the CEBQ subscale z-scores were significantly (p≤ 0.05) correlated with monthly headache frequency. Based on this finding the hypothesis of "z-scores for food responsiveness (FR), emotional overeating (EOE), enjoyment of food (EF) and desire to drink (DD) subscales of the CEBQ will have a significantly (p≤ 0.05) positive correlation with monthly headache frequency" was rejected. The hypothesis of "z-scores for satiety responsiveness (SR), slowness of eating (SE), emotional under eating (EUE) and food fussiness (FF) subscales of the CEBQ will have a significantly (p≤ 0.05) negative correlation with monthly headache frequency" was also rejected.

CEBQ subscale	**PedMIDAS r_s (p-value)**	**Monthly Headache Frequency r_s (p-value)**
Food Responsiveness	0.24 (0.14)	0.21 (0.20)
Emotional Over Eating	0.26 (0.11)	0.23 (0.16)
Enjoyment of Food	0.15 (0.36)	0.21 (0.20)
Desire to Drink	0.41 (0.01)*	0.22 (0.17)
Satiety Responsiveness	0.01 (0.95)	-0.12 (0.45)
Slowness of Eating	-0.15 (0.36)	-0.20 (0.22)
Emotional Under Eating	0.29 (0.07)	0.03 (0.88)
Food Fussiness Z-Score	0.15 (0.35)	-0.17 (0.32)

Table 3.5.6- Results for each of the CEBQ subscale spearman rank correlations with PedMIDAS scores and monthly headache frequency. *= significant finding (p≤ 0.05).

Distribution of z scores/raw scores according to the migraine groups

Standardised z-scores for each subscale of the CEBQ were plotted as histograms according to the four PedMIDAS migraine severity grades and three monthly headache frequency groups, which can be seen in figures 3.5.10 to 3.5.25.

As illustrated by figures 3.5.10, 3.5.11, 3.5.16 and 3.5.17, the mean z-scores for food responsiveness and desire to drink subscales increased with each migraine severity grade and headache frequency group. Grade I migraine severity (PedMIDAS scores< 10) and monthly headache frequency group 1 each had the lowest mean z-score for the emotional overeating and the enjoyment of food subscales (see figures 3.5.12 to 3.5.15). As illustrated by figures 3.5.18 and 3.5.19, satiety responsiveness had the highest mean z-score in migraine severity grade II (11 to 30 PedMIDAS scores), and in monthly headache frequency group 2 (4 to 10 monthly headaches). Figures, 3.5.20 and 3.5.21 demonstrate the slowness of eating mean z-scores were highest in migraine severity grade I and in the second monthly headache frequency group (<4 monthly headaches). The mean emotional under-eating z-scores were highest in the migraine severity grade III and in the monthly headache frequency group 3 (see figures 3.5.22 and 3.5.23). Mean food fussiness z-scores were highest in migraine severity grade IV and in monthly headache frequency group 1 (see figures 3.5.24 and 3.5.25).

Figure 3.5.10
A histogram to show the distribution of the food responsiveness (FR) z-scores as mean values among the four migraine severity grades

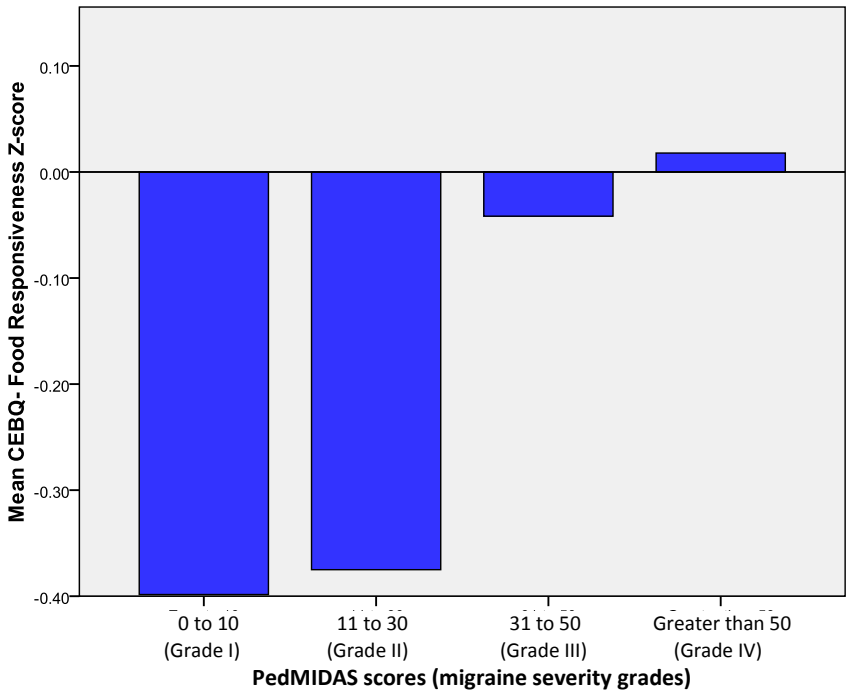


Figure 3.5.11
A histogram to show the distribution of the food responsiveness (FR) z-scores as mean values among the three monthly headache frequency groups

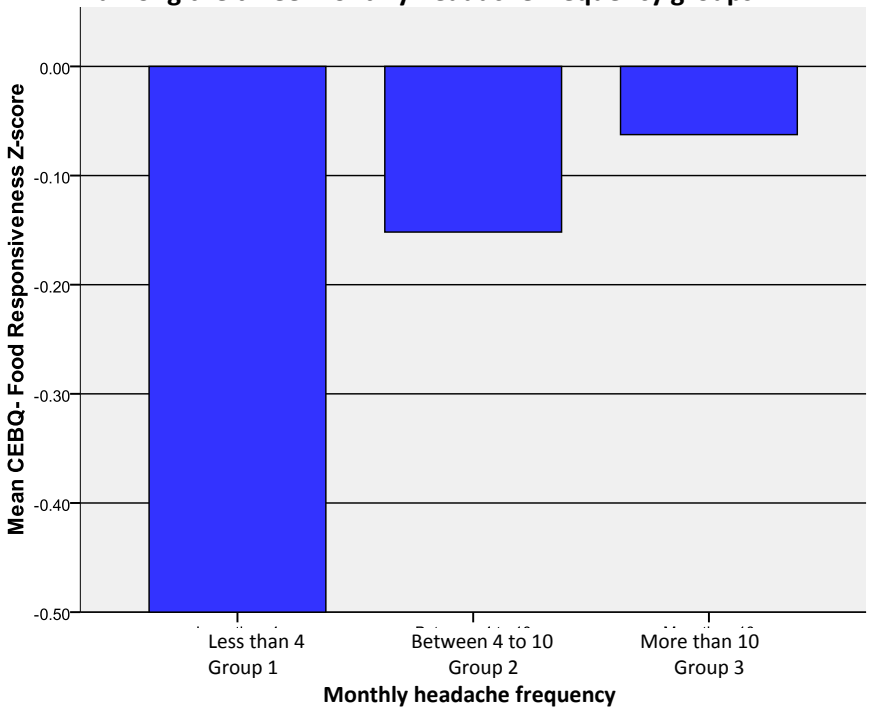


Figure 3.5.12
A histogram to show the distribution of the emotional over-eating (EOE) z-scores as mean values among the four migraine severity grades

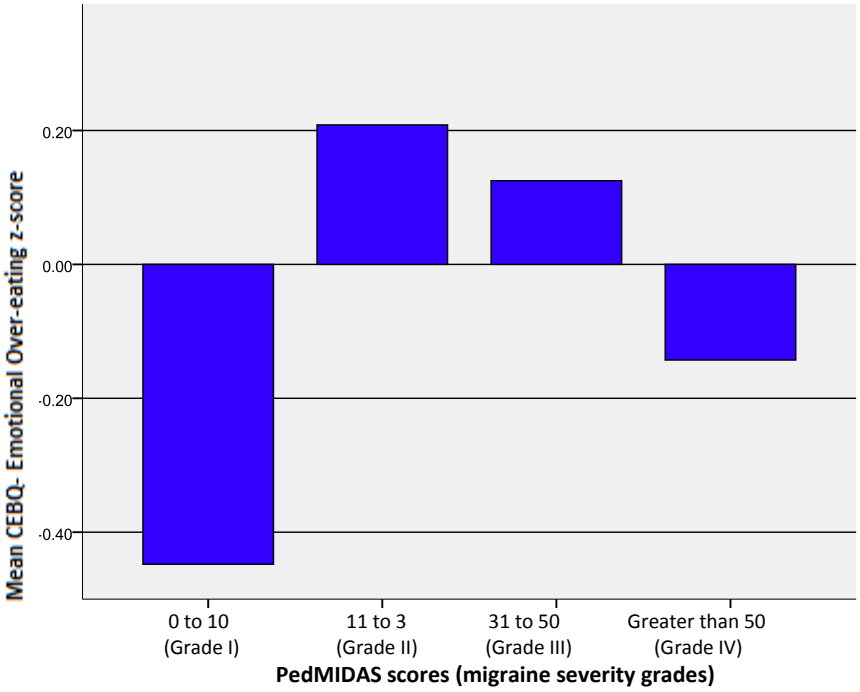


Figure 3.5.13
A histogram to show the distribution of the emotional over-eating (EOE) z-scores as mean values among the three monthly headache frequency groups

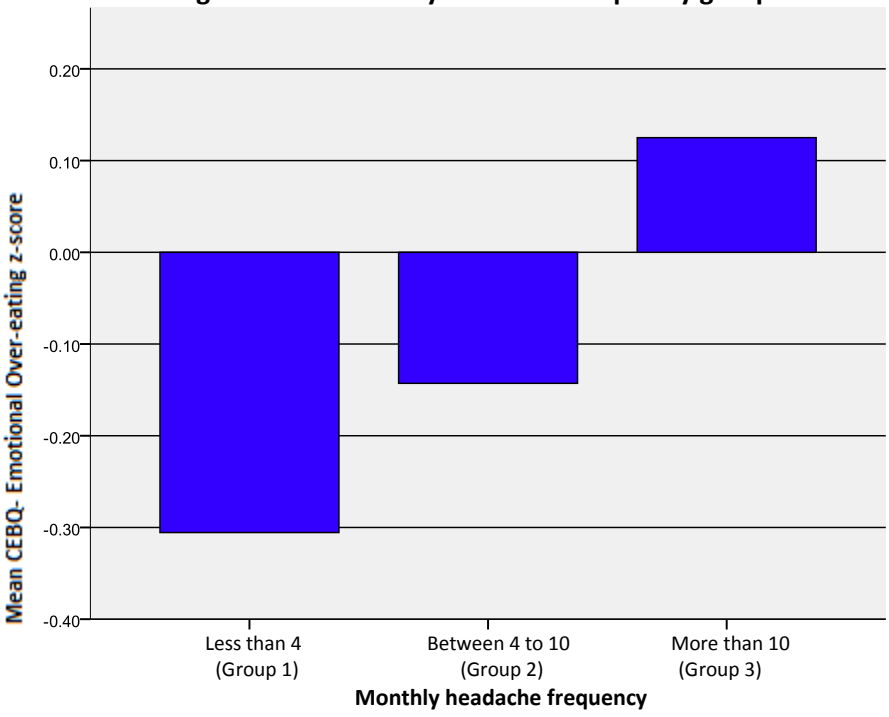


Figure 3.5.14
A histogram to show the distribution of the enjoyment of food (EF) z-scores as mean values among the four migraine severity grades

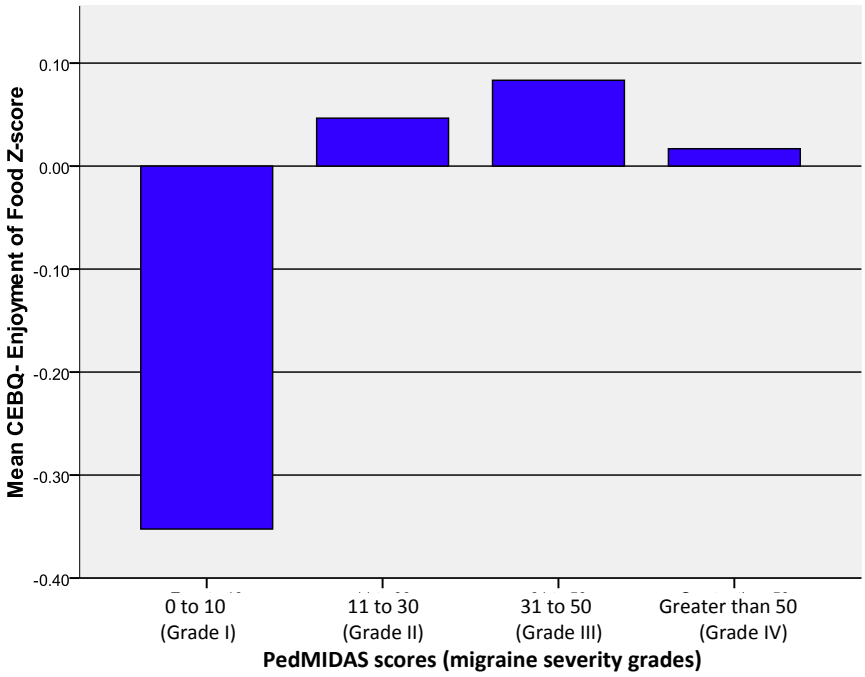


Figure 3.5.15
A histogram to show the distribution of the enjoyment of food (EF) z-scores as mean values among the three monthly headache frequency groups

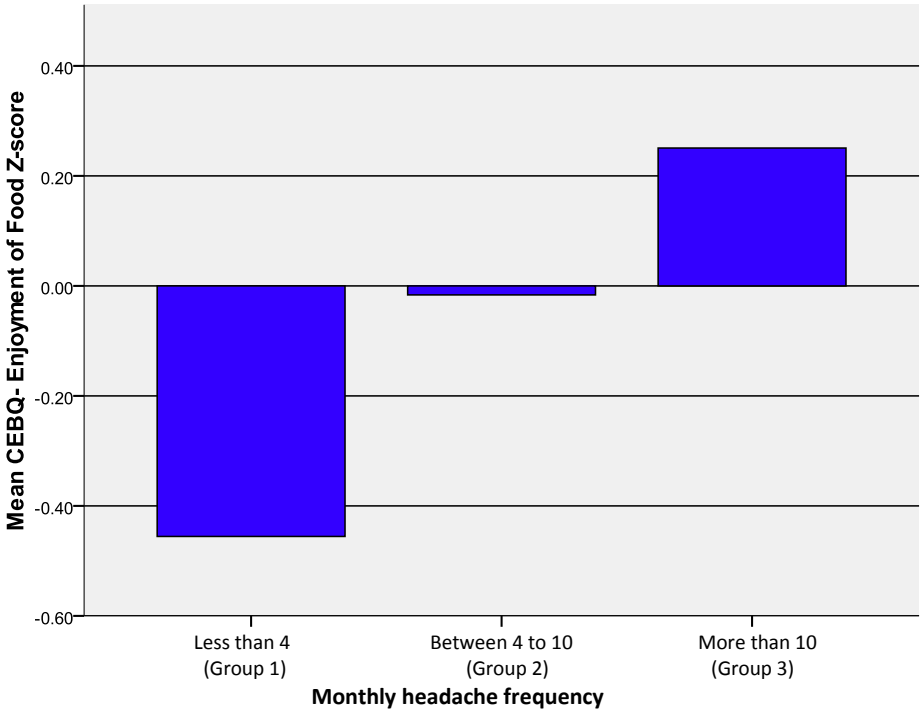


Figure 3.5.16
A histogram to show the distribution of the desire to drink (DD) z-scores as mean values among the four migraine severity grades

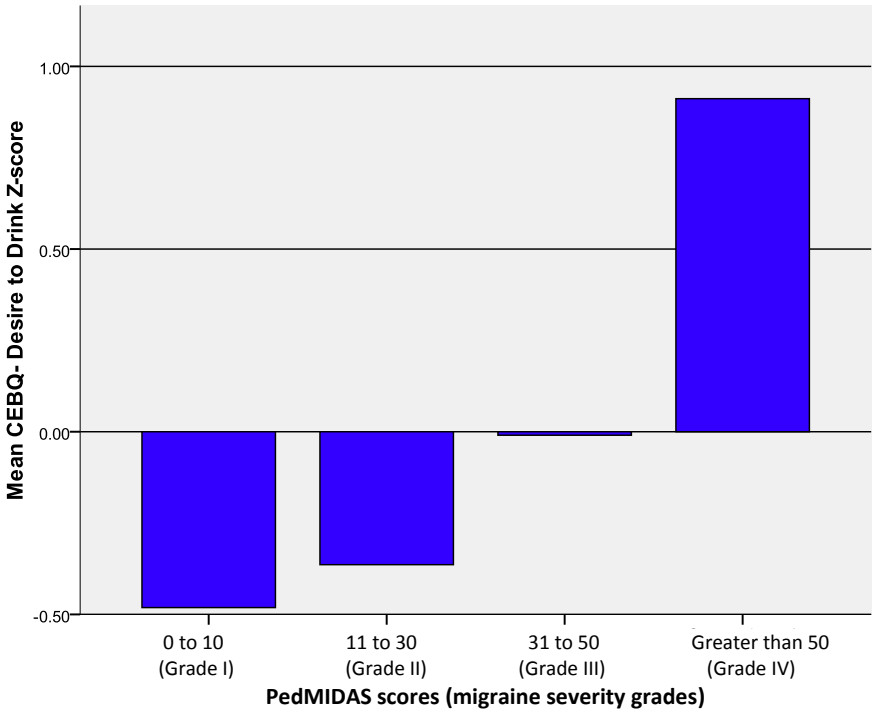


Figure 3.5.17
A histogram to show the distribution of the desire to drink (DD) z-scores as mean values among the three monthly headache frequency groups

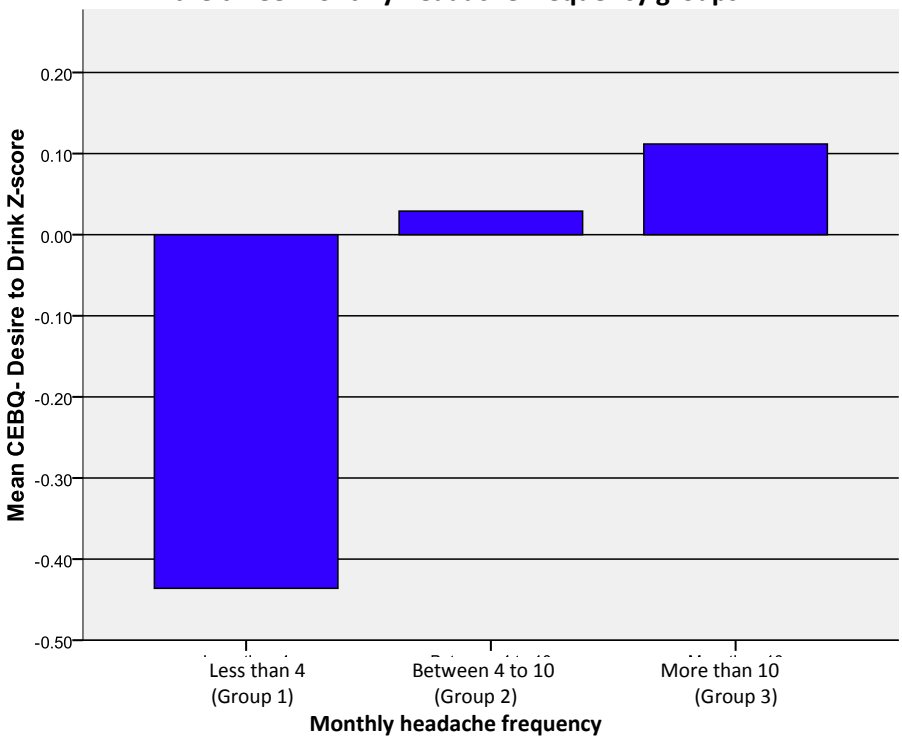


Figure 3.5.18
A histogram to show the distribution of the satiety responsiveness (SR) z-scores as mean values among the four migraine severity grades

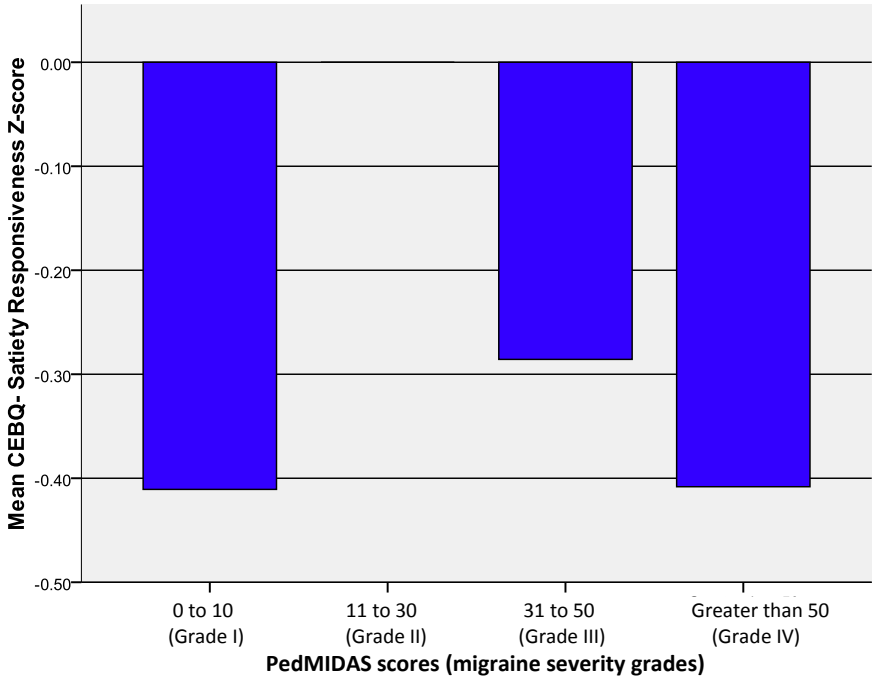


Figure 3.5.19
A histogram to show the distribution of the satiety responsiveness (SR) z-scores as mean values among the three monthly headache frequency groups

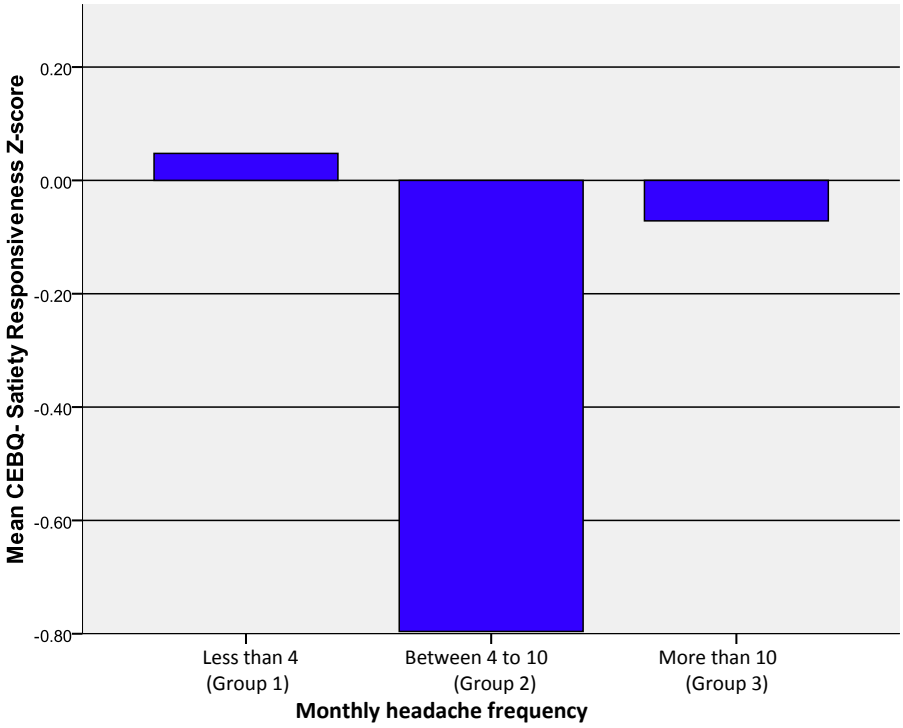


Figure 3.5.20
A histogram to show the distribution of the slowness of eating (SE) z-scores as mean values among the four migraine severity grades

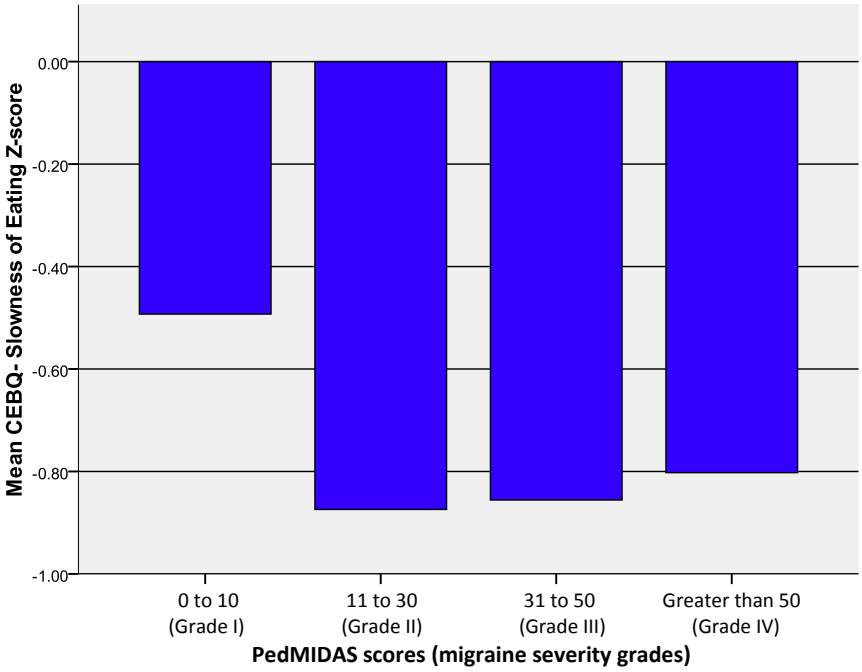


Figure 3.5.21
A histogram to show the distribution of the slowness of eating (SE) z-scores as mean values among the three monthly headache frequency groups

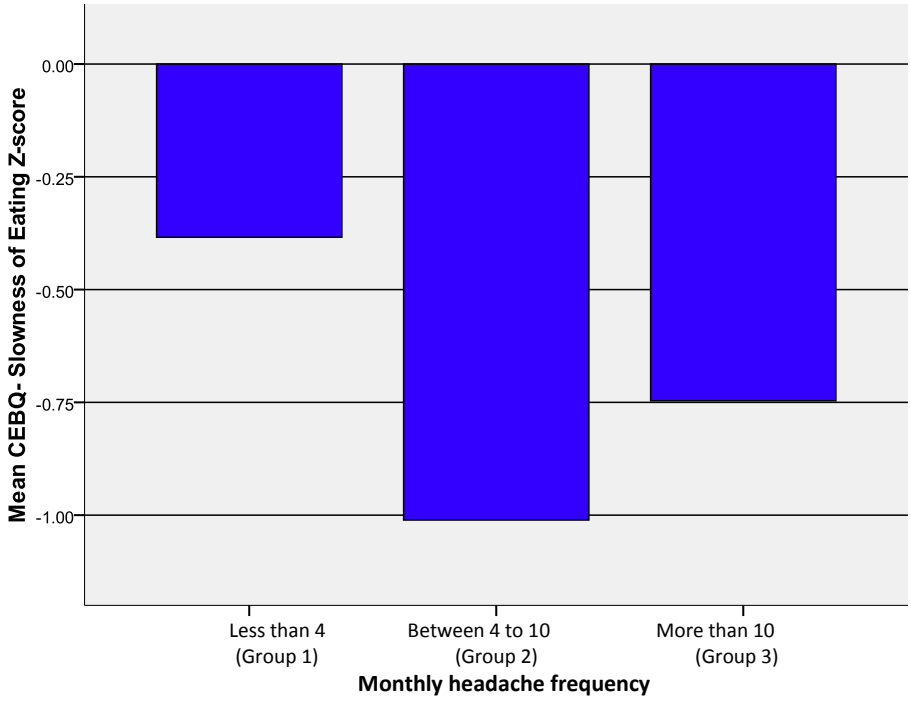


Figure 3.5.22
A histogram to show the distribution of the emotional under-eating (EUE) z-scores as mean values among the four migraine severity grades

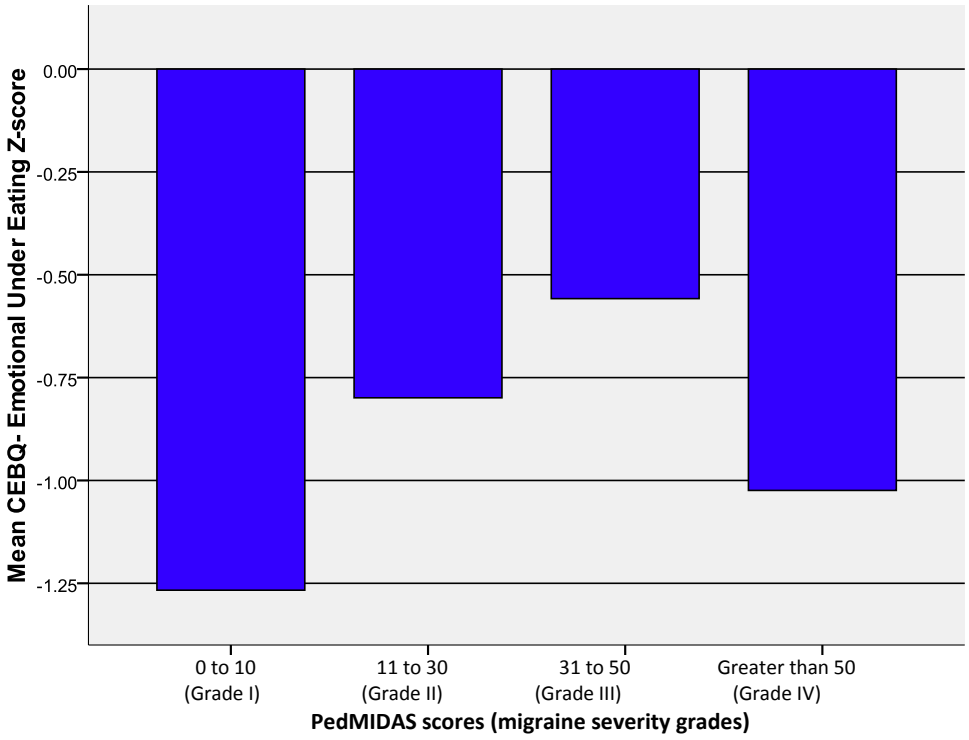


Figure 3.5.23
A histogram to show the distribution of the emotional under-eating (EUE) z-scores as mean values among the three monthly headache frequency groups

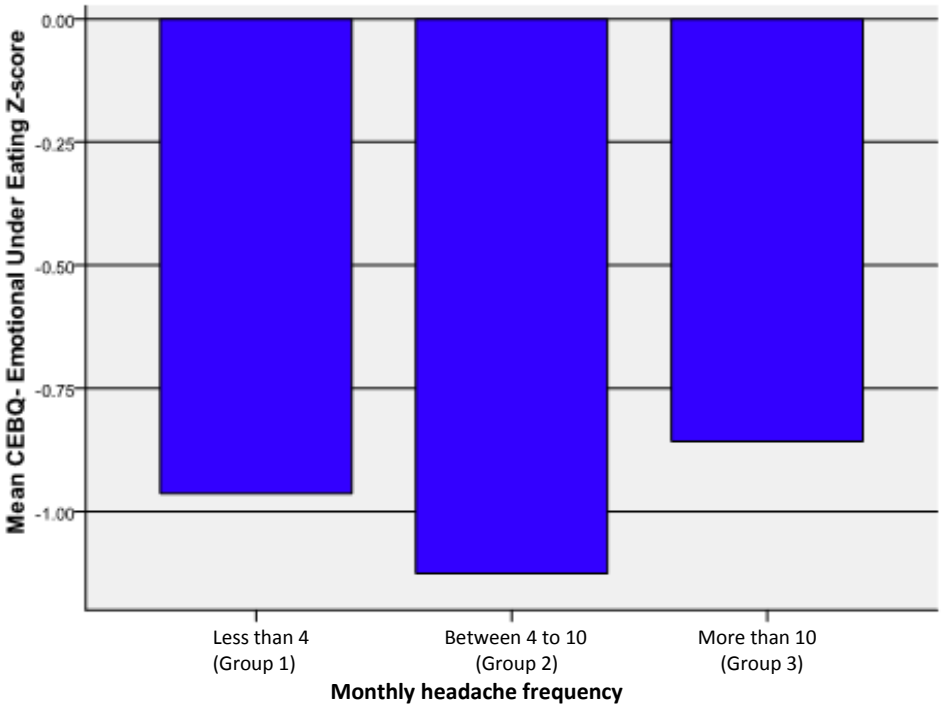


Figure 3.5.24
A histogram to show the distribution of the food fussiness (FF) z-scores as mean values among the four migraine severity grades

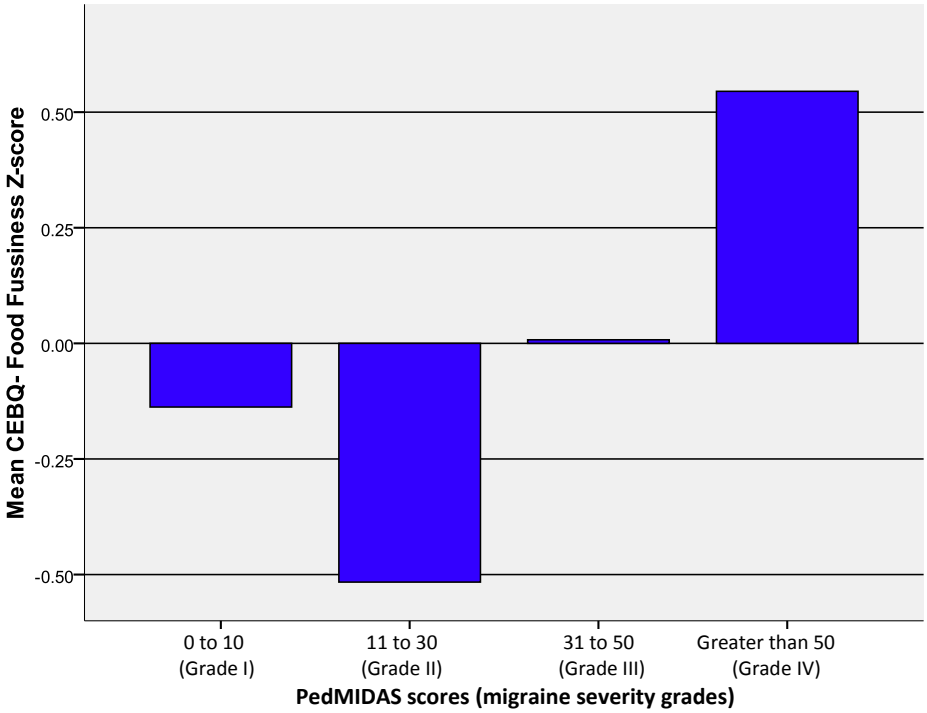
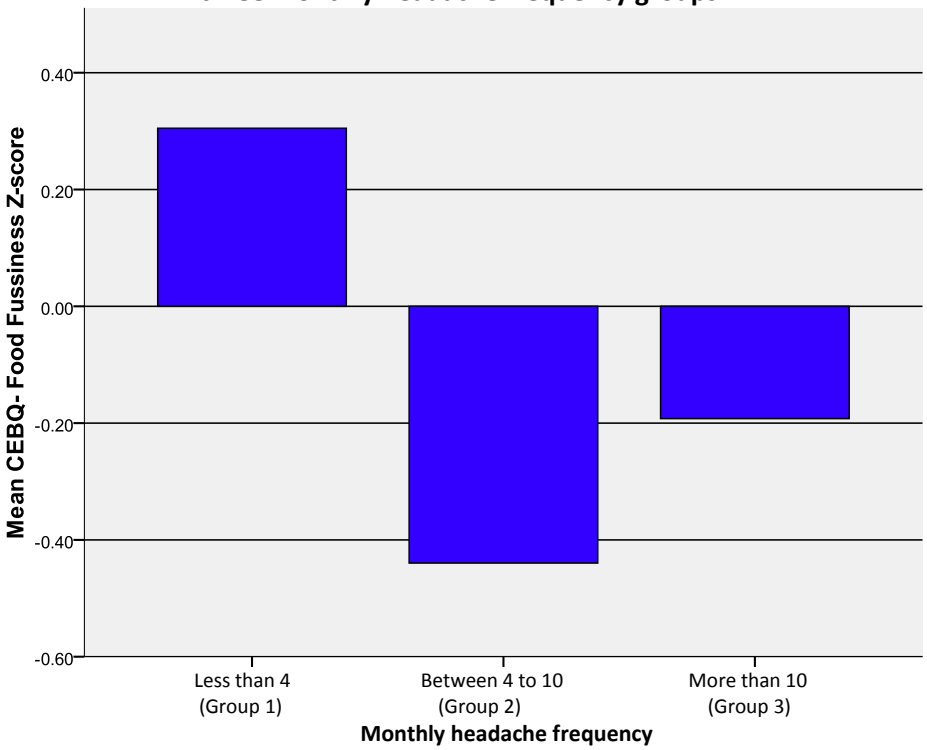


Figure 3.5.25
A histogram to show the distribution of the food fussiness (FF) z-scores as mean values among the three monthly headache frequency groups



Comparison of CEBQ z-scores between the four migraine severity grades

As can be seen from table 3.5.7, the chi-squared value for each subscale of the CEBQ was insignificant at the corrected probability level of 0.003, indicating that none of the CEBQ subscale z-scores significantly differed between the four migraine severity grades. For this reason the hypothesis of "CEBQ subscale (FR/EOE/DD/EF/SR/SE/EUE/FF) z-scores will significantly ($p<0.003$) differ between the four grades of migraine severity (I, II, II, IV)" was rejected.

CEBQ Subscale	Grouping variable: PedMIDAS migraine severity grades Chi-square value (p-value)
Food Responsiveness (FR) z-scores	2.87 (0.41)
Emotional Over Eating (EOE) z-scores	2.17 (0.54)
Enjoyment of Food (EF) z-scores	1.43 (0.69)
Desire to Drink (CEBQ scores)	9.57 (0.02)
Satiety Responsiveness (SR) z-scores	0.87 (0.83)
Slowness of Eating (SE) z-scores	0.70 (0.87)
Emotional Under Eating (EUE) z-scores	1.96 (0.58)
Food Fussiness (FF) z-scores	2.91 (0.40)

Table 3.5.7- Kruskal-Wallis test results for comparison of CEBQ subscale z-scores between the four migraine severity grades

Comparison of CEBQ z-scores between the three monthly headache frequency groups

As can be seen from table 3.5.8, the chi squared value for each subscale of the CEBQ was insignificant at the corrected probability level of 0.003, indicating that none of the CEBQ subscale z-scores significantly differed between the three monthly headache frequency groups. For this reason the hypothesis, "CEBQ subscale (FR/EOE/DD/EF/SR/SE/EUE/FF) z-scores will significantly ($p<0.003$) differ between the three groups of headache frequency (groups 1-3)" was rejected.

CEBQ Subscale	Grouping variable: Monthly Headache frequency groups Chi-square value (p-value)
Food Responsiveness (FR) z-scores	1.82 (0.40)
Emotional Over Eating (EOE) z-scores	2.25 (0.33)
Enjoyment of Food (EF) z-scores	1.47 (0.48)
Desire to Drink (CEBQ scores)	2.29 (0.32)
Satiety Responsiveness (SR) z-scores	4.27 (0.12)
Slowness of Eating (SE) z-scores	2.39 (0.30)
Emotional Under Eating (EUE) z-scores	0.31 (0.86)
Food Fussiness (FF) z-scores	2.57 (0.28)

Table 3.5.8- Kruskal-Wallis test results for comparison of CEBQ subscale z-scores between the three monthly headache frequency groups

CEBQ subscale z-score correlations with CBCL subscale T-scores

As can be seen from table 3.5.9, there were no significant correlations (at the probability level of 0.05) between any of the CEBQ subscale z-scores and CBCL subscale T-scores. For this reason the hypothesis that "CBCL subscale T-scores will have a significantly ($p \leq 0.05$) positive correlation with food responsiveness, emotional overeating, enjoyment of food and desire to drink subscales of the CEBQ", was rejected. The hypothesis that "CBCL subscale T-scores will have a significantly ($p<0.05$) negative correlation with satiety responsiveness, slowness of eating, emotional under-eating and food fussiness subscales of the CEBQ" was also rejected.

CEBQ Subscale	Externalised T-scores r_s *(p- value)*	Internalised T-scores r_s *(p- value)*	Total T-scores r_s *(p- value)*
FR z-scores	0.17 (0.30)	0.18 (0.27)	0.16 (0.33)
EOE z-scores	0.10 (0.54)	0.20 (0.22)	0.04 (0.81)
EF z-scores	0.00 (0.10)	-0.65 (0.69)	0.18 (0.91)
DD z-scores	0.20 (0.23)	0.17 (0.30)	0.13 (0.45)
SR z-scores	0.05 (0.79)	0.15 (0.36)	0.04 (0.81)
SE z-scores	-0.13 (0.43)	0.16 (0.34)	-0.05 (0.76)
EUE z-scores	0.05 (0.78)	0.26 (0.11)	0.09 (0.59)
FF z-scores	0.06 (0.69)	0.02 (0.92)	-0.06 (0.73)

Table 3.5.9- Correlations between CEBQ subscale z-scores and CBCL subscale T-scores.

Chapter 3.6

Food cravings inventory (FCI-II) results

All 60 patients that were recruited completed the food cravings inventory (FCI-II). The raw FCI-II scores produced from each subscale were used in the study analyses. Standardised z-values were not calculated because there were no normal range reference values based on child population samples. However mean adult FCI-II age specific results from a study by Burton et al[212] were used as reference values (as outlined in table 3.6.2) that were compared with the mean FCI-II raw scores produced in this pilot study.

Distribution of the food cravings inventory (FCI-II) raw scores

Data for the high fats, carbohydrates and fast food fat subscales followed a parametric distribution, while data for the sweets subscale was of a non-parametric distribution. The mean raw scores for each FCI-II subscale as calculated from the total patient sample (n= 60) are listed in table 3.6.1. The mean score for the high fats subscale was 1.92, which was the exact same value as the reference mean score for the high fats subscale (see table 3.6.2). The overall mean score for the fast food fats subscale was 2.55, which was higher than the reference fast food fats mean value of 1.91.

The mean score for the sweets subscale at 2.31 was higher than the respective reference mean of 2.05. The mean score for the carbohydrates subscale at 2.39 was higher than the respective reference mean 2.22. Further details on the distribution of the FCI-II subscale raw scores can be seen in table 3.6.1.

Categories	FCI-II- High Fats raw mean scores	FCI-II- Sweets raw mean scores	FCI-II- Carbohydrates raw mean scores	FCI-II- Fast Food Fats raw mean scores
Mean	1.92	2.31	2.39	2.55
Std. Deviation	0.69	0.85	0.89	1.03
Median	1.94	2.25	2.38	2.50
Minimum	1.00	1.00	1.00	1.04
Maximum	3.50	4.38	4.30	5.03

Table 3.6.1- Distribution of FCI-II subscale raw scores for all 60 patients recruited

FCI-II Subscale	Mean reference score
High fats	1.93
Sweets	2.05
Carbohydrates	2.22
Fast food fats	1.91

Table 3.6.2- Mean FCI-II subscale reference values

Category	Characteristic	N	High Fats Mean (s.d)	Sweets Mean (s.d)	Carbohydrates Mean (s.d)	Fast food fats Mean (s.d)
Gender	*Female*	34	1.78 (0.64)	2.22 (0.70)	2.30 (0.79)	2.43 (0.96)
	Male	26	2.10 (0.73)	2.40 (1.00)	2.51 (1.02)	2.70 (1.12)
Age	*6 - 12 years*	37	1.99 (0.76)	2.37 (1.00)	2.42 (0.96)	2.66 (1.15)
	13 -16 years	23	1.80 (0.58)	2.20 (0.60)	2.35 (0.79)	2.38 (0.82)

Table 3.6.3- Mean FCI-II subscale raw scores according to age and gender

As can be seen in table 3.6.3, for every subscale of the FCI-II, the mean male raw score was greater than the mean female raw score. The greatest gender difference in mean raw scores was for high fat foods (male mean = 2.1; female mean = 1.78). The average score for every subscale was higher among younger children aged 6 to 12 years compared with older patients aged 13 to 16 years. The greatest difference between these two age groups was within the fast food fats subscale; children aged 6-12 years had a mean score of 2.66 versus 2.38 in children aged 13 to 16 years.

Box plots for the distribution of FCI-II high fat (figure- 3.6.1), sweet food (figure- 3.6.2), carbohydrate (figure- 3.6.3) and fast food fat (fig- 3.6.4) food scores, each display a positively skewed appearance.

Figure 3.6.1- A box plot to illustrate the distribution of the FCI-II high fat food scores

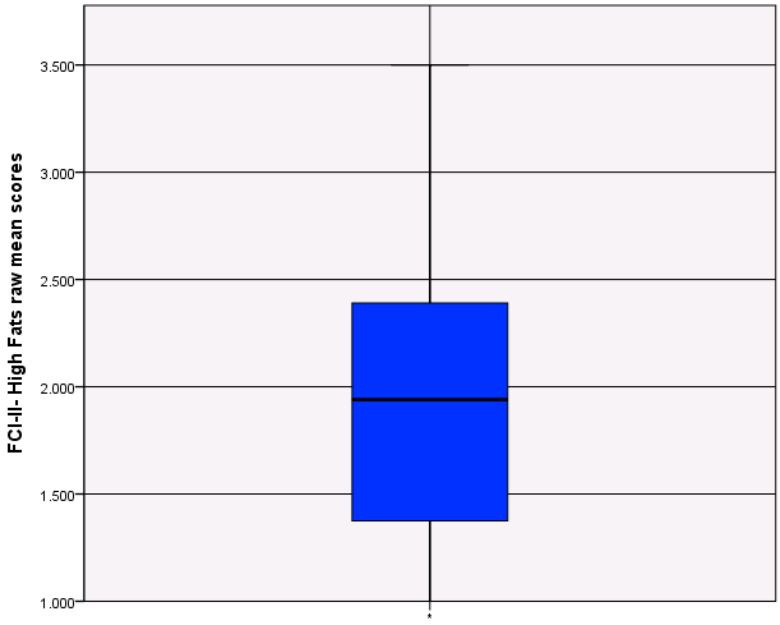


Figure 3.6.2- A box plot to illustrate the distribution of the FCI-II sweet food scores

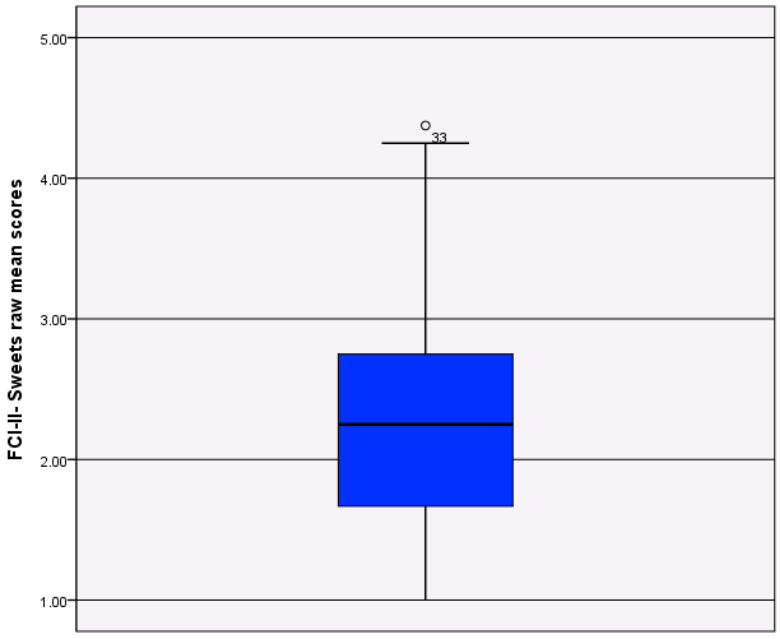


Figure 3.6.3- A box plot to illustrate the distribution of the FCI-II carbohydrate food scores

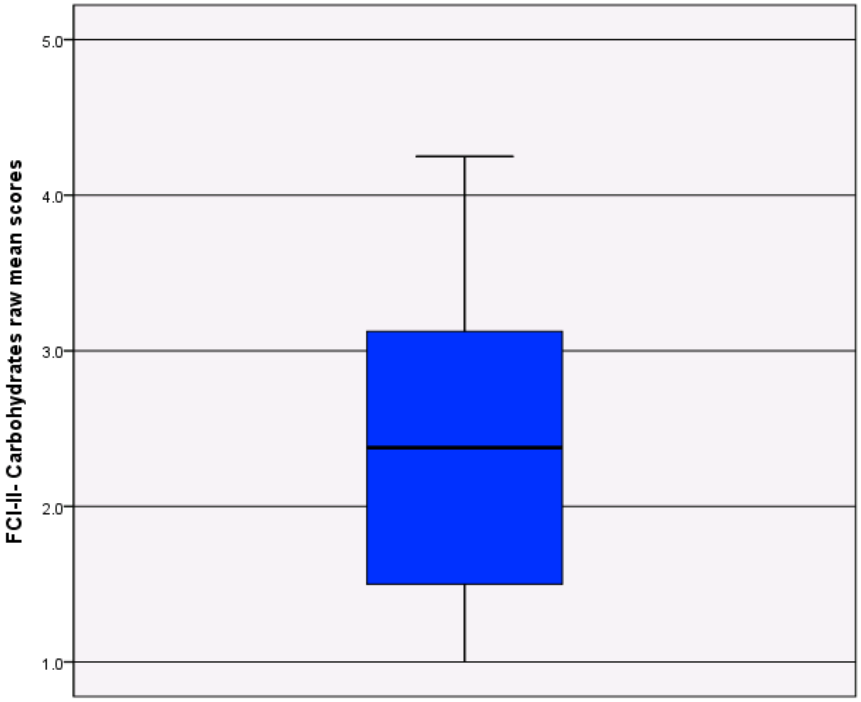
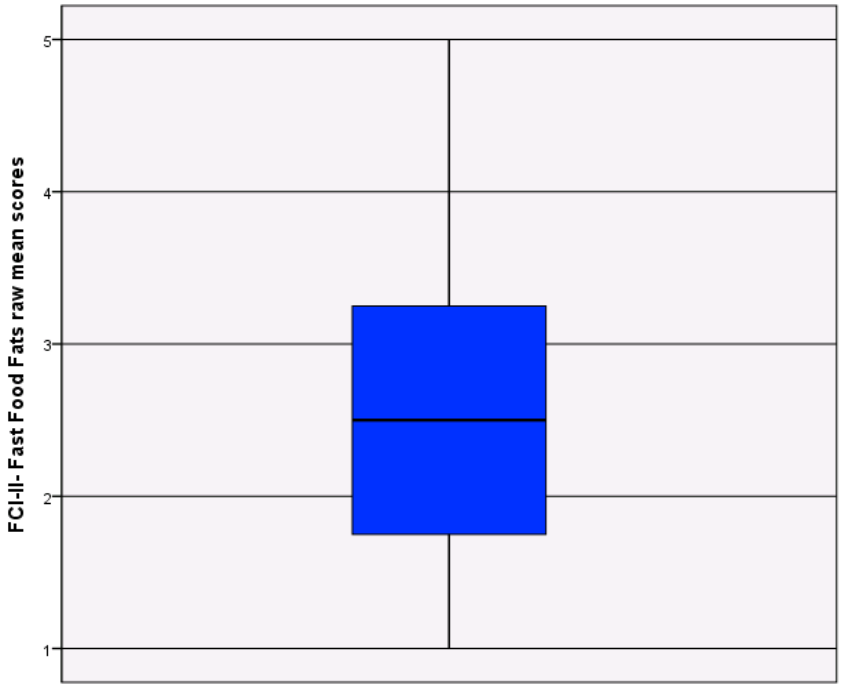


Figure 3.6.4- A box plot to illustrate the distribution of the FCI-II fast food fat scores



Frequency of patients with raw scores below/above reference ranges

As can be seen in table 3.6.4, there was an equal distribution of patients with a raw score above and below the reference mean for the high fats subscale. There were a slightly higher proportion of patients that had raw scores above the reference mean than below it, in the sweets and carbohydrates FCI-II subscales. In the fast food fats subscale two thirds (n=20) of the total sample had a raw score above the reference mean.

FCI-II sub scale	Frequency of patients with raw scores below reference mean (% of N= 60)	Frequency of patients with raw scores above reference mean (% of N= 60)
High fats	30 (50)	30 (50)
Sweets	25 (42)	35 (58)
Carbohydrates	27 (45)	33 (55)
Fast food fats	20 (33)	40 (67)

Table 3.6.4- Frequency of patients with FCI-II subscale raw scores below or above the reference mean scores

Correlations between FCI-II raw scores and PedMIDAS scores

As outlined in table 3.6.5, there were no significant ($p \leq 0.05$) correlations between any of the FCI-II subscales and PedMIDAS migraine severity scores. For this reason the hypothesis that "the FCI-II subscale scores (high fat/sweet/carbohydrate/fast food fats) will have a significantly ($p \leq 0.05$) positive correlation with the PedMIDAS (migraine severity) scores" was rejected.

Correlations between FCI-II raw scores and monthly headache frequency

As outlined in table 3.6.5, none of the FCI-II subscales were significantly ($p \leq 0.05$) correlated with the monthly headache frequency values. For this reason the hypothesis that "the FCI-II subscale scores (high fat/sweet/carbohydrate/fast food fats) will have a significantly ($p \leq 0.05$) positive correlation with the monthly headache frequency values" was rejected.

FCI-II subscale	PedMIDAS r_s (p-value)	Headache Frequency r_s (p-value)
FCI-II- High Fats	-0.03 (0.83)	-0.02 (0.90)
FCI-II- Sweets	0.07 (0.59)	0.01 (0.93)
FCI-II- Carbohydrates	0.12 (0.37)	-0.09 (0.48)
FCI-II- Fast Food Fats	0.05 (0.71)	-0.05 (0.71)

Table 3.6.5- Spearman's rank correlation results between the FCI-II subscale raw scores and the PedMIDAS migraine severity scores/ monthly headache frequency values

Distribution of raw scores according to the migraine groups

Mean FCI-II subscale scores were grouped according to the four grades of PedMIDAS migraine severity and the three groups of monthly headache frequency. Histograms were drawn to illustrate the distributions of FCI-II subscale scores according to these migraine groups, which can be seen in figures 3.6.5 to 3.6.12.

High fat FCI-II scores showed little variation in mean values when grouped according to the four migraine severity grades and three headache frequency groups (figures 3.6.5 and 3.6.6). Figure 3.6.8 shows the highest mean FCI-II sweets score was in grade II (mild migraine severity; 11-30 PedMIDAS scores), whilst in figure 3.6.7, the highest FCI-II sweets score was in monthly headache frequency group 3 (>10 monthly headaches). Figure 3.6.9 shows that the highest FCI-II carbohydrate foods score was in the lowest headache frequency group (< 4 monthly headaches). Figure 3.6.10 shows the highest FCI-II carbohydrate food scores were in the second and third migraine severity grades. Mean FCI-II fast food fat scores decreased with every headache frequency group as illustrated by figure 3.6.11, but increased with every migraine severity grade up until grade III, as outlined by figure 3.6.12.

Figure 3.6.5
A histogram to display the distribution of the high fat food (FCI-II) scores according to the three headache frequency groups

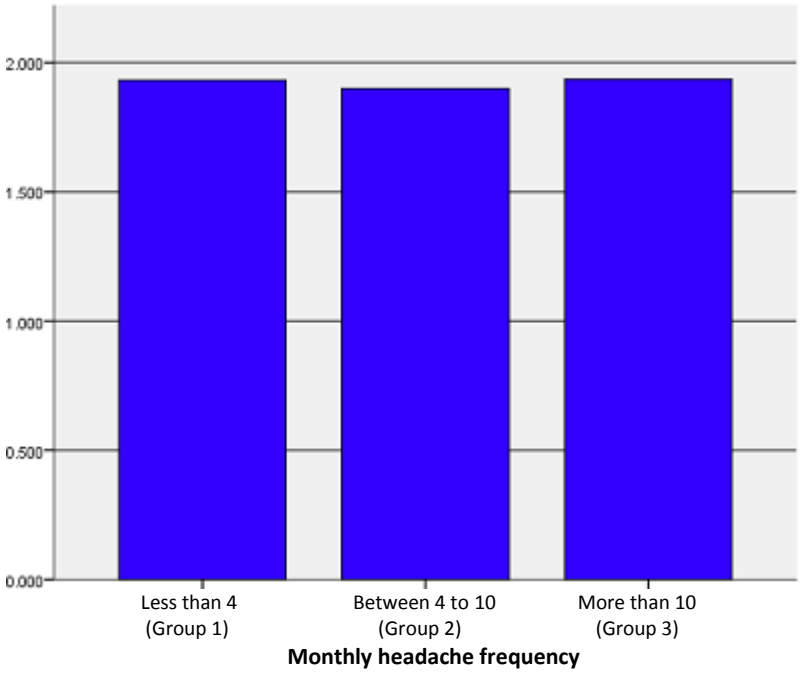


Figure 3.6.6
A histogram to display the distribution of the high fat food (FCI-II) scores according to the four migraine severity grades

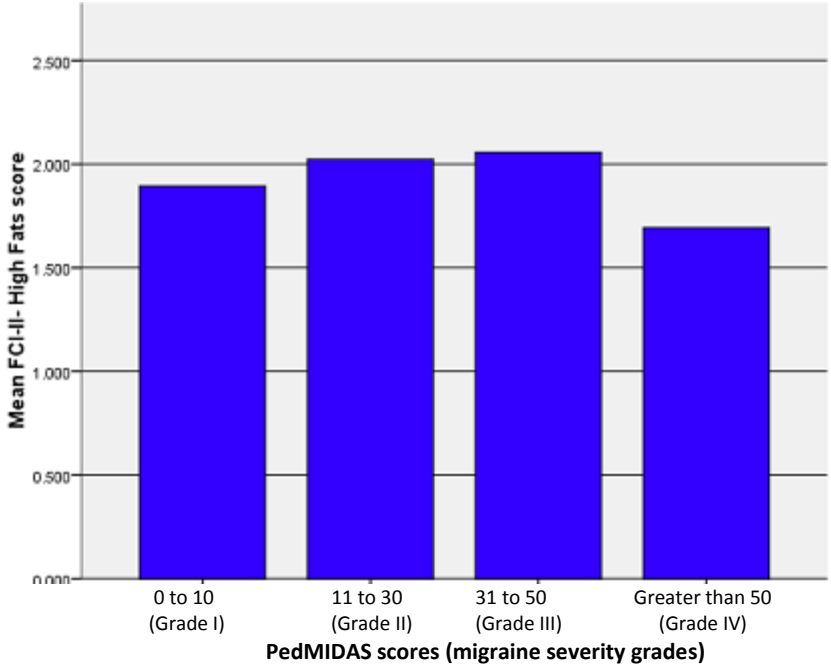


Figure 3.6.7
A histogram to display the distribution of the sweet food (FCI-II) scores according to the three headache frequency groups

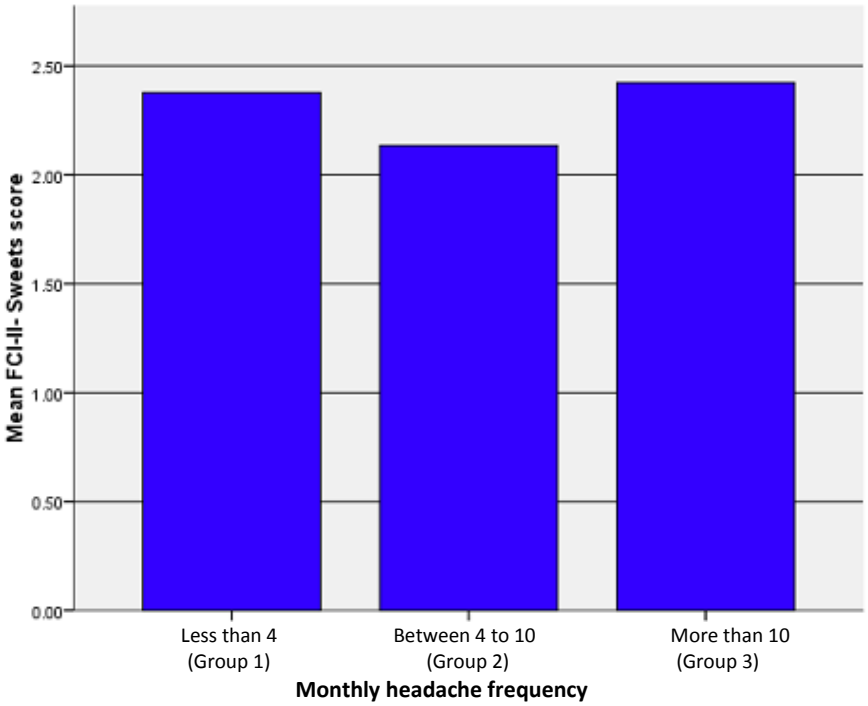


Figure 3.6.8
A histogram to display the distribution of the sweet food (FCI-II) scores according to the four migraine severity grades

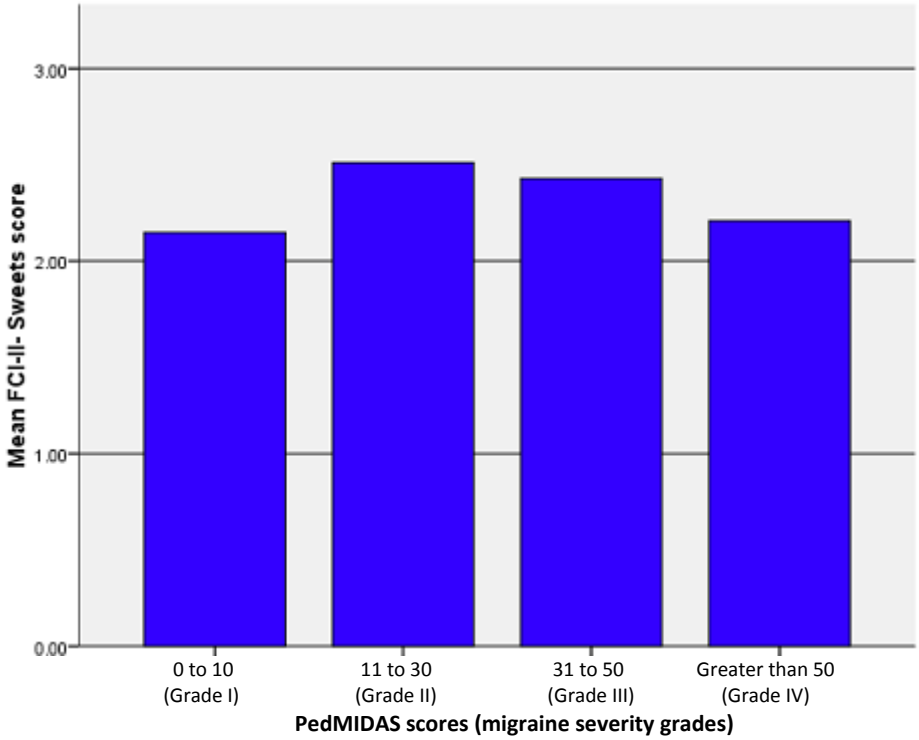


Figure 3.6.9
A histogram to display the distribution of the carbohydrate food (FCI-II) scores according to the three monthly headache frequency groups

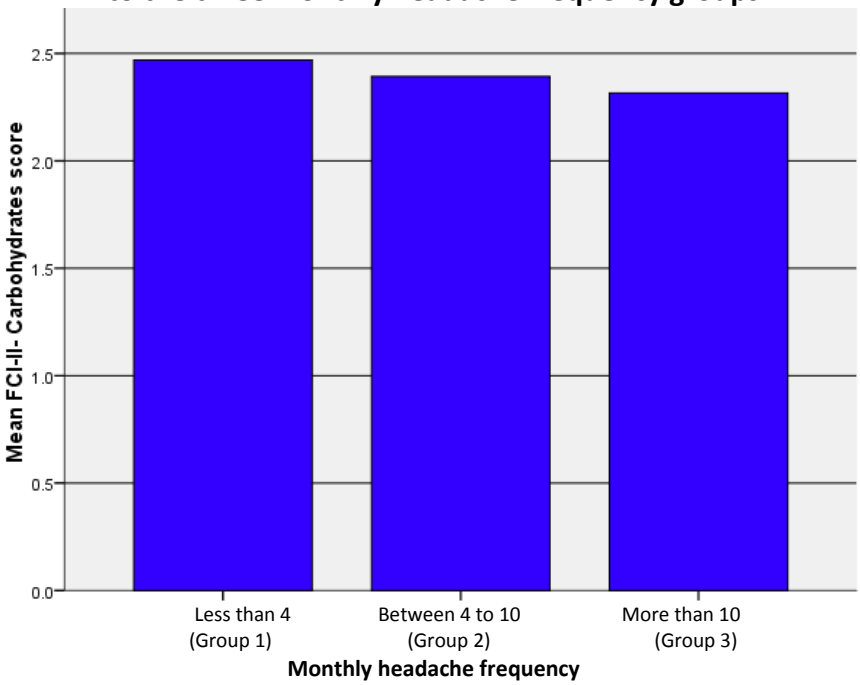


Figure 3.6.10
A histogram to display the distribution of the carbohydrate food (FCI-II) scores according to the four migraine severity grades

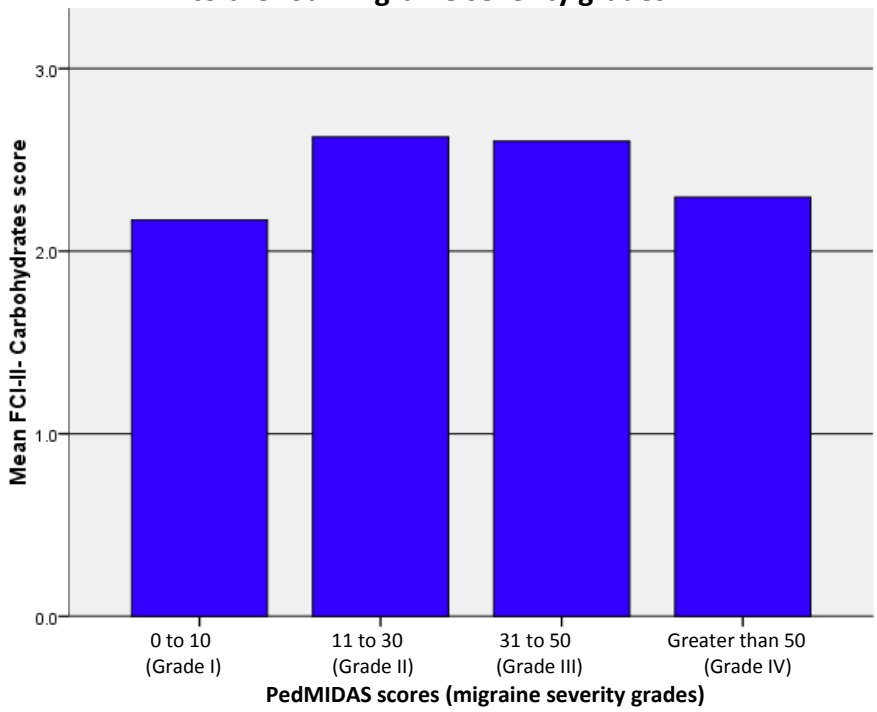


Figure 3.6.11
A histogram to display the distribution of the fast food fat (FCI-II) scores according to the three monthly headache frequency groups

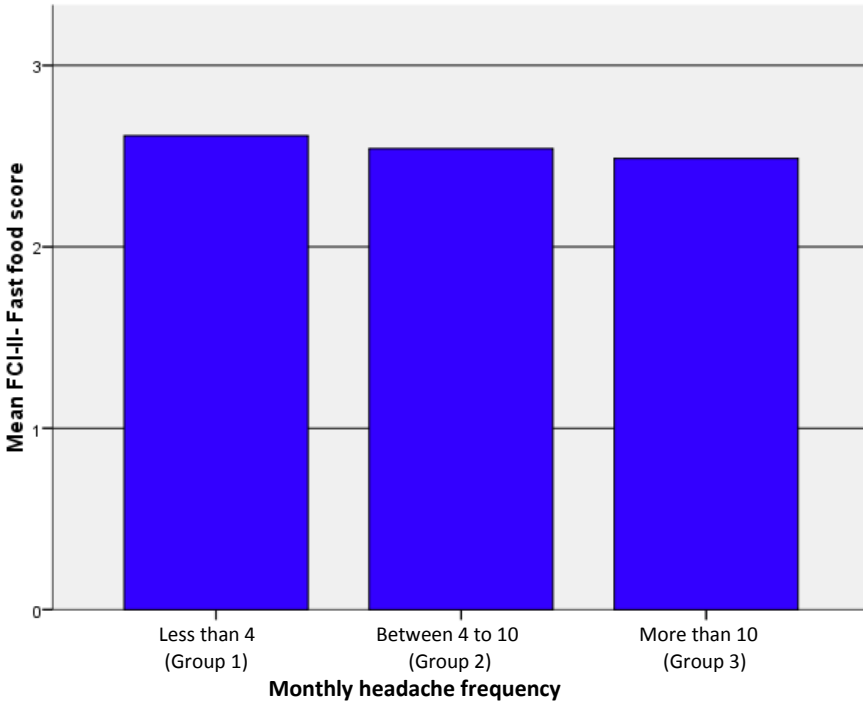
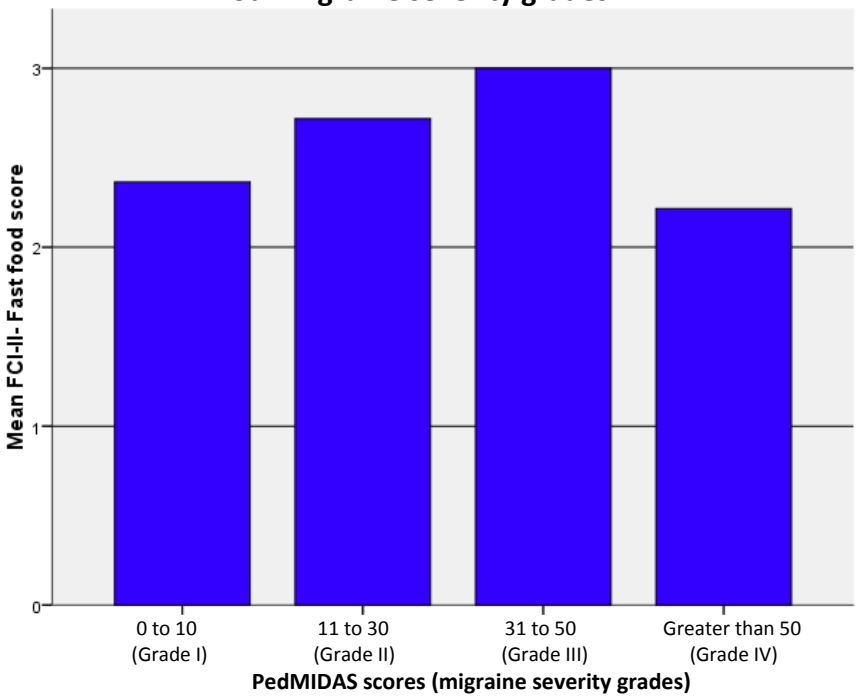


Figure 3.6.12
A histogram to display the distribution of the fast food fat (FCI-II) scores according to the four migraine severity grades



Comparison of the FCI-II subscale scores between the four migraine severity grades

As can be seen in table 3.6.6, the chi-square values for each FCI-II subscale were insignificant at the corrected probability level of 0.006. For this reason the hypothesis that "the FCI-II subscale scores (high fat/sweets/carbohydrates/fast food fats) will significantly differ between the four different grades of PedMIDAS migraine severity", was rejected.

Comparison of the FCI-II subscale scores between the three monthly headache frequency groups

As can be seen in table 3.6.6, the chi-square values for each FCI-II subscale were insignificant at the corrected probability level of 0.006. For this reason the hypothesis that "the FCI-II subscale scores (high fat/sweets/carbohydrates/fast food fats) will significantly differ between the three monthly headache frequency groups", was rejected.

FCI-II subscale	PedMIDAS (migraine severity) grades	Monthly Headache Frequency categories
	Chi-square (p-value)	Chi-square (p-value)
High Fats	1.99 (0.57)	0.12 (0.94)
Sweets	0.95 (0.81)	0.88 (0.65)
Carbohydrates	2.78 (0.43)	0.19 (0.91)
Fast Food Fats	3.63 (0.30)	0.09 (0.96)

Table 3.6.6- Kruskal-Wallis test results for the comparison of FCI-II subscale scores between the four PedMIDAS migraine severity grades and the three monthly headache frequency groups

FCI-II Correlations with the Child Behaviour Checklist (CBCL) T-scores

As outlined in table 3.6.7, none of the FCI-II subscales were significantly ($p \leq 0.05$) correlated with any of the CBCL subscale T-scores. Based on this finding the hypothesis that "the FCI-II subscale scores will have a significantly positive correlation with all of the CBCL subscale T-scores (externalised/ internalised/ total)" was rejected.

FCI-II Subscale	CBCL Externalised T-scores r_s (p-value)	CBCL Internalised T-scores r_s (p-value)	CBCL Total T-scores r_s (p-value)
High Fats	0.14 (0.30)	0.02 (0.91)	0.09 (0.48)
Sweets	0.08 (0.52)	0.08 (0.53)	0.10 (0.43)
Carbohydrates	0.15 (0.25)	0.04 (0.77)	0.12 (0.36)
Fast Food Fats	0.07 (0.62)	0.07 (0.61)	0.07 (0.58)

Table 3.6.7- Spearman's rank correlation results for the CBCL subscale T-scores and FCI-II subscale scores

Chapter 3.7

Food Intake Questionnaire (FIQ) results

Distribution of raw scores

All 60 patients that were recruited in this pilot study completed the FIQ tool. It must be noted that the FIQ scores represented the number of food items eaten in each FIQ subscale. It must also be noted that the FIQ negative marker subscale was a combination of the negative sugary food subscale and negative fatty food subscale. Table 3.7.1, lists the mean raw score for each FIQ subscale as calculated from the total sample of 60 patients. The mean FIQ score of 8 for the negative marker food subscale was very close to the respective

median value of 7. In the negative marker food subscale the minimum score reported was zero and a maximum score reported was 26; this produced the greatest range of scores compared with any other FIQ subscale, which was expected considering the negative marker food subscale contained the most number of food items. The mean negative sugary and negative fatty scores were both the same at a value of 4. The mean positive fibre food score was very low (mean= 1). The mean positive marker food subscale score was equal to the respective median value (mean/median= 4).

Statistical description	Neg- marker foods	Neg- sugary foods	Neg- fatty foods	Pos+ marker foods	Pos+ fibre foods
Mean (s.d)	8 (4)	4 (2)	4 (3)	4 (2)	1 (1)
Median	7	3	3	4	0
Minimum	0	0	0	0	0
Maximum	26	9	14	12	4

Table 3.7.1- Distributions of FIQ subscale scores

Mean raw scores were plotted on box plots to display the distribution of data for each FIQ subscale. Figures 3.7.2 (negative sugary foods) and 3.7.5 (positive high fibre foods) each display a positively skewed distribution of FIQ scores. The box plot for negative fatty food scores (figure 3.7.2) illustrates a mild negatively skewed distribution of FIQ scores. Figures, 3.7.1 (negative marker foods) and 3.7.4 (positive marker foods), do not have a skewed appearance of FIQ scores. Data for the negative sugary food and positive marker food subscales each followed a parametric distribution. Data for the other FIQ subscales followed a non-parametric distribution.

Figure 3.7.1 -Box plot to display the distribution of Negative marker food scores

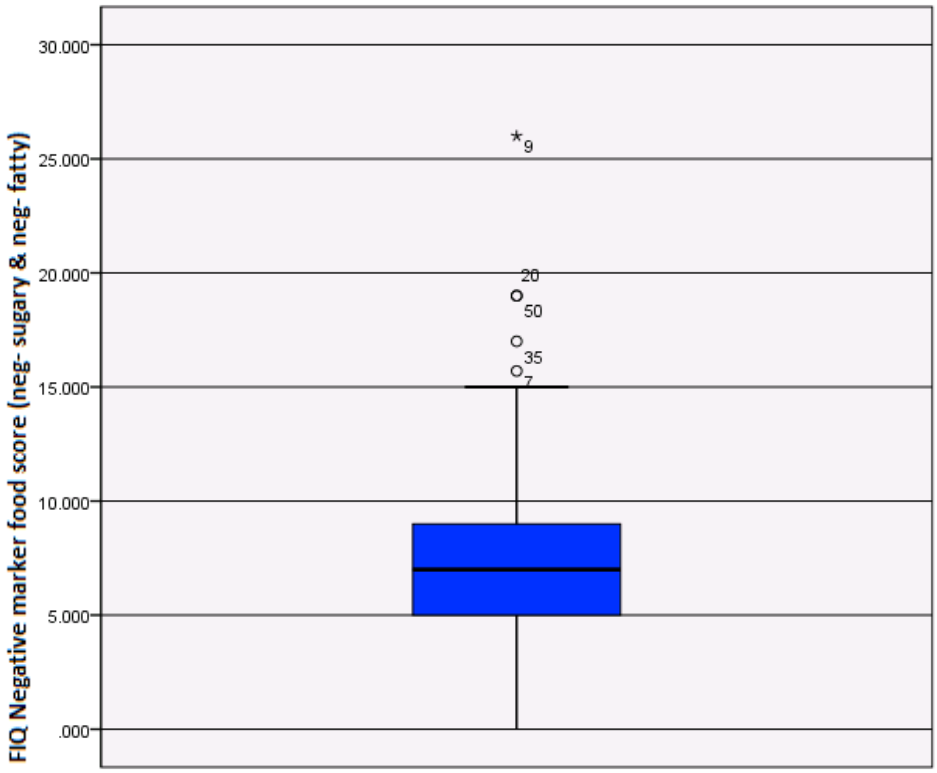


Figure 3.7.2- Box plot to display the distribution of negative sugary food scores

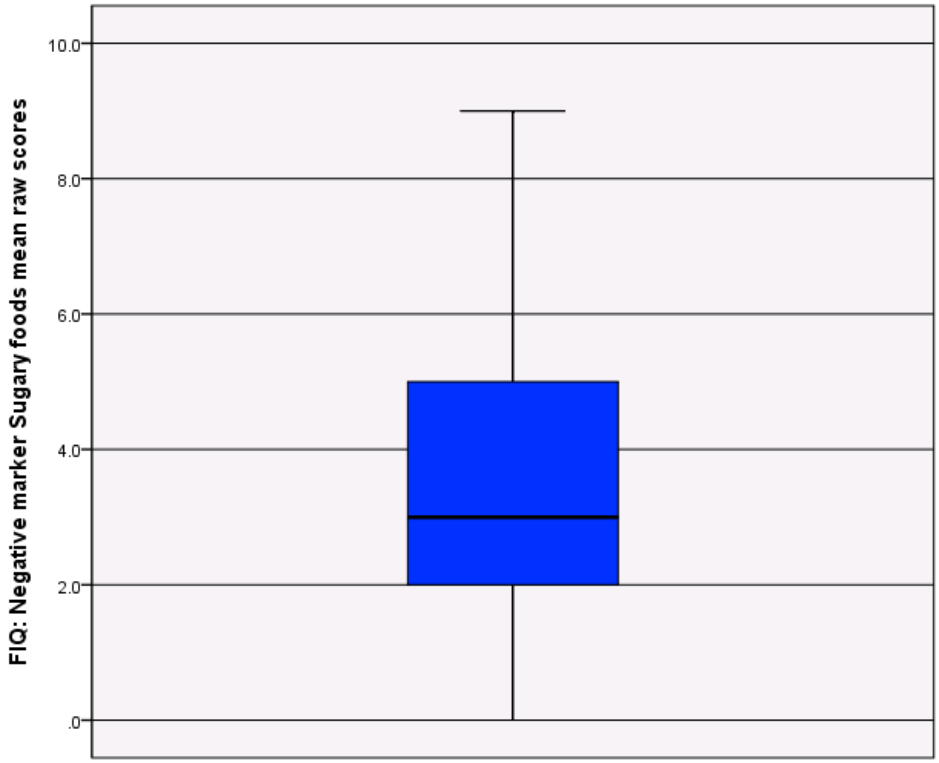


Figure 3.7.3- Box Plot to display the distribution of Negative marker Fatty Food scores

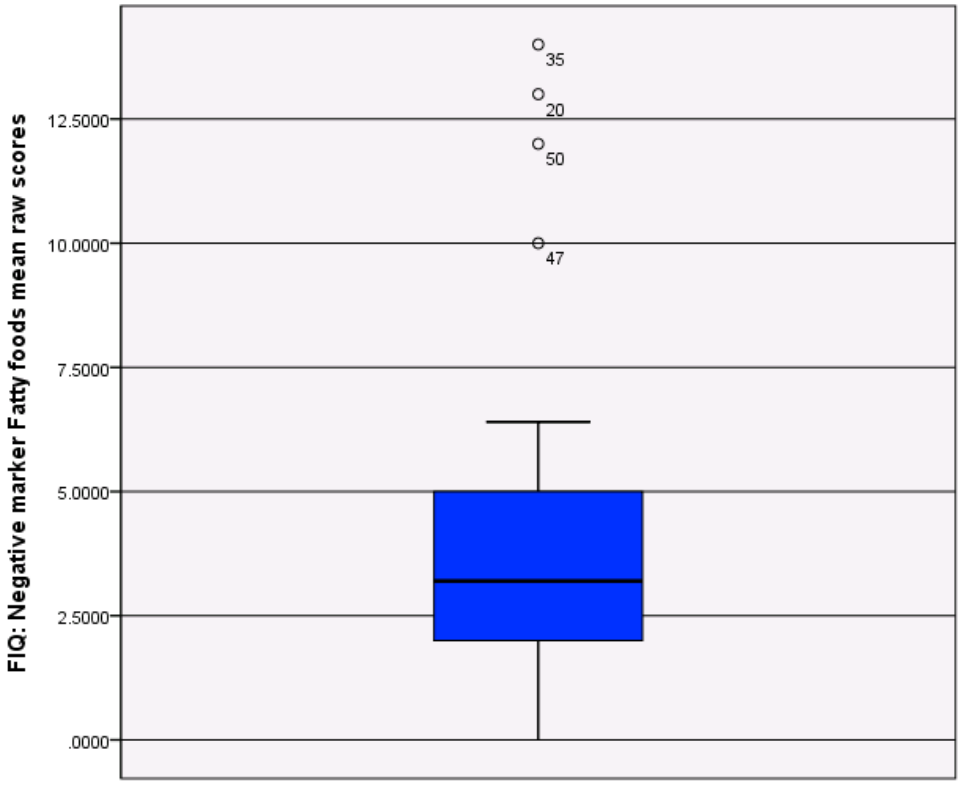


Figure 3.7.4- Box plot to show the distribution of positive marker food scores

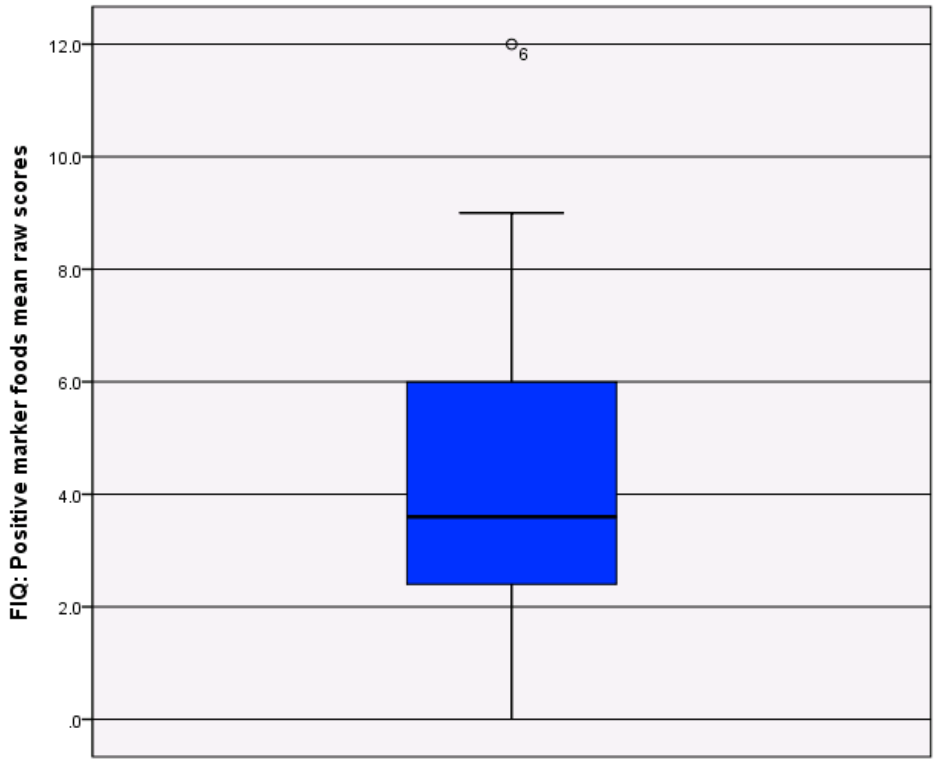
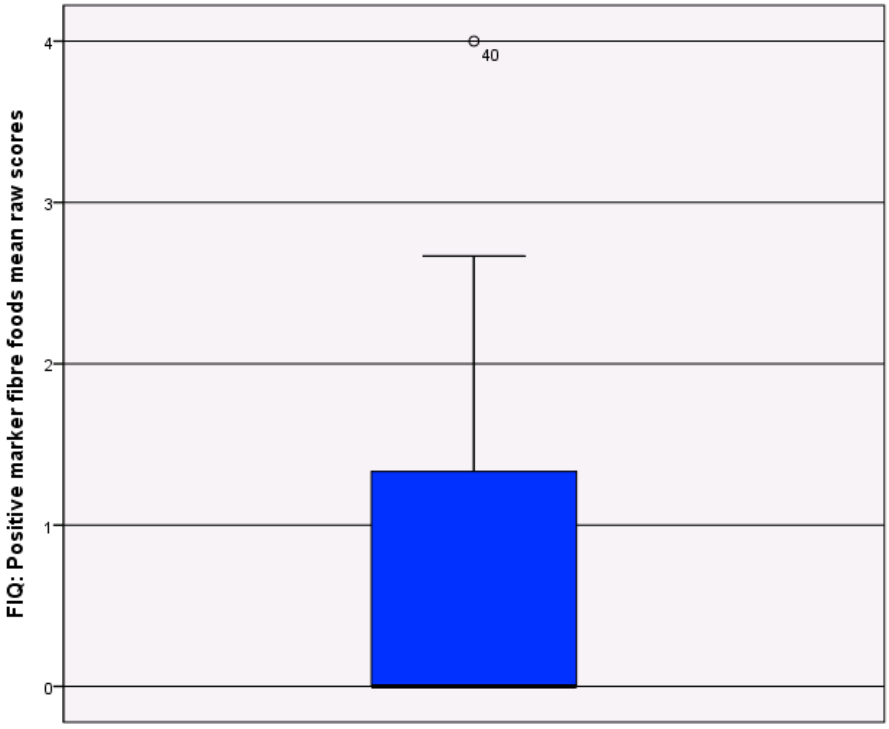


Figure 3.7.5- Box plot to show the distribution of Positive high fibre food scores



Raw scores according to age and gender

As can be seen in table 3.7.2, the mean FIQ negative sugary food score for children aged 13 to 16 years (mean= 4) was slightly higher than that for children aged 5 to 12 years (mean= 3). Conversely, the mean FIQ positive marker food score for children aged 13 to 16 years (mean= 3) was slightly lower than that for children aged 5 to 12 years (mean= 4). The mean negative sugary foods score for boys (mean= 4) was slightly higher than that for girls (mean= 3). None of the mean scores from the other subscales differed according to age and gender groupings.

Categories	Neg- marker mean (s.d)	Neg- Sugary mean (s.d)	Neg- Fatty mean (s.d)	Pos+ marker mean (s.d)	Pos+ Fibre mean (s.d)
5-12 years	8 (5)	3 (2)	4 (3)	4 (2)	1 (1)
13-16 years	8 (4)	4 (2)	4 (3)	3 (2)	1 (1)
Female	8 (5)	3 (2)	4 (3)	4 (3)	1 (1)
Male	8 (3)	4 (1)	4 (3)	4 (2)	1 (1)

Table 3.7.2- Distribution of FIQ subscale scores according to age and gender

Frequency of patients with FIQ raw scores below/above reference mean

FIQ data from this pilot study were compared with reference data from a study that tested the validity of the FIQ. The reference data was based on a sample of 98 children aged 13-14 years attending two schools in deprived areas of Liverpool, England[174]. Table 3.7.4 outlines the reference values. Table 3.7.3 lists the frequency of patients in this pilot study with a FIQ score that was above or below the references mean values. It shows that for each FIQ subscale the majority of patients in this pilot study had a FIQ raw score that was below the reference mean. However for negative fatty foods, 29 patients (48%) had a FIQ raw score that was higher than the reference mean.

FIQ subscale	Frequency of patients below reference mean N (% of N= 60)	Frequency of patients above reference mean N (% of N= 60)
Neg- marker	53 (88)	7 (12)
Neg- Sugary	58 (97)	2 (3)
Neg- fatty	31 (52)	29 (48)
Pos+ marker	49 (82)	11 (18)
Pos+ fibre	56 (93)	4 (7)

Table 3.7.3- Frequency of patients with a raw score above or below the reference mean

FIQ Subscale	No of food items in each subscale	Mean reference values
Neg- marker	29	13
Neg- sugary	12	8
Neg- fatty	16	3
Pos+ marker	18	6
Pos+ fibre	4	2

Table 3.7.4- A list of mean reference values for each FIQ subscale
*Reference values were extrapolated from a FIQ validity study by Johnson et al[174]

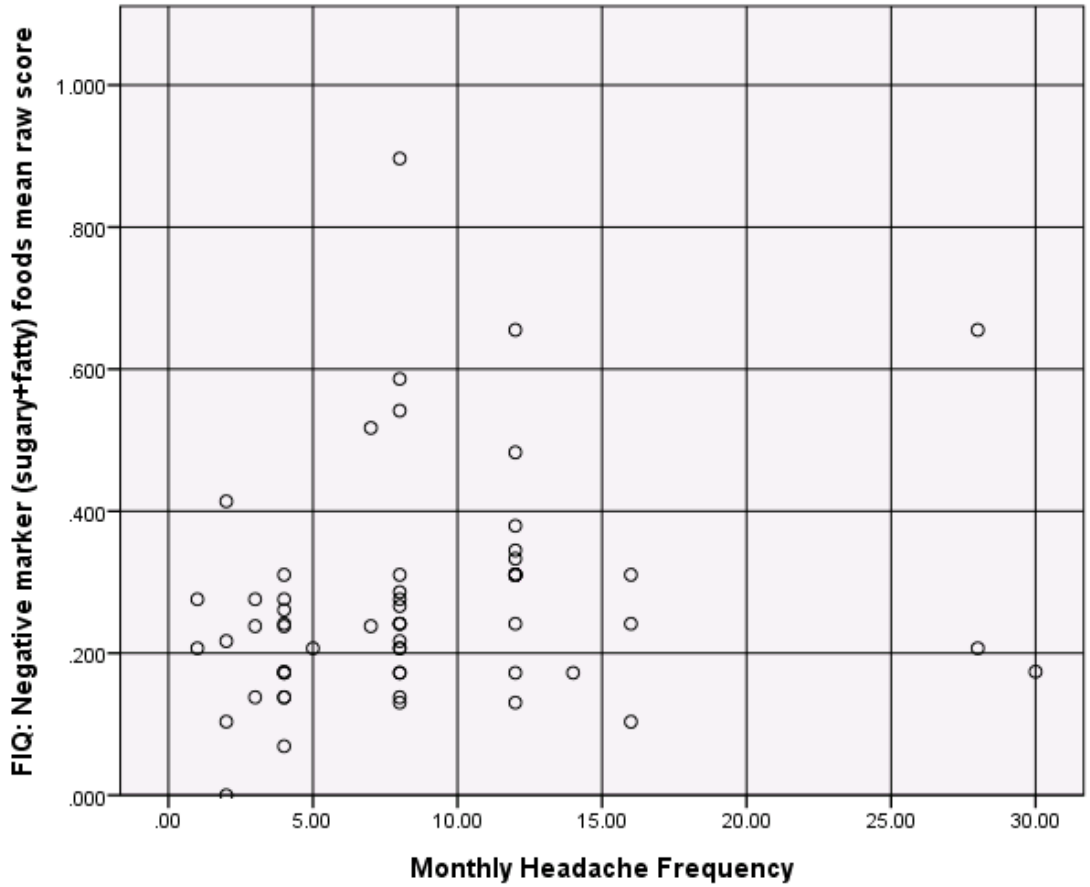
Correlation between FIQ subscale scores and PedMIDAS scores

As outlined in table 3.7.5, none of the FIQ subscale scores were significantly ($p \leq 0.05$) correlated with the PedMIDAS scores. For this reason the hypothesis that "the PedMIDAS scores will have a significantly ($p \leq 0.05$) positive correlation with the FIQ negative marker, negative sugary and negative fatty food scores" was rejected. The hypothesis that "the PedMIDAS scores will have a significantly ($p \leq 0.05$) negative correlation with the FIQ positive marker and positive fibre food scores", was also rejected.

Correlation between FIQ subscale scores and monthly headache frequency

As outlined in table 3.7.5, there was a weak but significant ($p \leq 0.05$) positive correlation between the FIQ negative marker food subscale and monthly headache frequency ($r_s = 0.27$; p-value= 0.04). Based on this finding the hypothesis that "negative marker FIQ scores will have a significant ($p \leq 0.05$) positive correlation with monthly headache frequency" was accepted. On advice from the statistician involved in this pilot study, a correlation coefficient equal to or greater than 0.7 was considered a strong correlation. Given that the correlation coefficient (r_s) was 0.27 the correlation between the FIQ negative marker food subscale and monthly headache frequency was considered to be quite weak. This point is further demonstrated in figure 3.7.6 by the weak association of dots in the scatter graph of FIQ negative marker food scores plotted against the monthly headache frequency values.

Figure 3.7.6- Scatter graph of the FIQ negative marker food scores plotted against the monthly headache frequency values



As can be seen in table 3.7.5 the remaining FIQ subscale scores were not significantly ($p \leq 0.05$) correlated with the monthly headache frequency values. For this reason the hypothesis that "the monthly headache frequency values will have a significant ($p \leq 0.05$) positive correlation with the FIQ negative sugary and the negative fatty food scores" was rejected. The hypothesis that "the monthly headache frequency values will have a significant ($p \leq 0.05$) negative correlation with the FIQ positive marker food scores and the positive fibre foods scores" was also rejected.

FIQ subscale	PedMIDAS r_s (p-value)	Headache Frequency r_s (p-value)
Negative Marker foods	0.05 (0.71)	0.27 (0.04)*
Negative maker sugary foods	0.08 (0.54)	0.25 (0.06)
Negative marker fatty foods	-0.11 (0.41)	0.17 (0.18)
Positive Marker foods	0.05 (0.73)	0.18 (0.17)
Positive marker fibre foods	0.10 (0.43)	0.01 (0.97)

Table 3.7.5- Results for Spearman's rank correlations made between the FIQ subscale scores and monthly headache frequency/ PedMIDAS severity scores. *= significant finding ($p \leq 0.05$)

Distribution of the FIQ subscale scores according to the migraine groups

Mean raw scores were calculated for each FIQ subscale according to the four migraine severity grades and the three monthly headache frequency groups; these can be seen in figures, 3.7.7 to 3.7.16. When grouped according to the migraine severity grades, the highest mean negative marker score was found in the fourth migraine severity grade (>50 PedMIDAS scores) as illustrated by figure 3.7.7. The highest mean in the negative sugary food and the negative fatty food subscales were each found in the third migraine severity grade, as can be seen in figures 3.7.8 and 3.7.9. The mean values for the positive marker food (figure 3.7.10) and the positive high fibre food (figure 3.7.11) subscales increase with each increment in migraine severity grade, up until grade III.

When categorised according to the monthly headache frequency groups, the mean scores for the negative marker food, negative sugary food and positive marker food subscales increased with each increment in monthly headache frequency group number; this is represented on the respective histograms (figures 3.7.12, 3.7.13 and 3.7.15) as a negatively skewed appearance. Figure 3.7.14 for the negative fatty food subscale shows the mean score peaks in the 4 to 10 monthly headache frequency group. Figure 3.7.16 for the positive high fibre food subscale shows the mean score peaks in the first monthly headache frequency group (< 4 headaches per month).

Figures, 3.7.7 and 3.7.12, show that the highest mean FIQ negative marker score was found in the 4th migraine severity grade (> 50 PedMIDAS scores) and in the 4 to 10 monthly headache frequency group. Mean scores for the negative sugary, negative fatty, positive marker and positive fibre food subscales were highest in the third migraine severity grade (31-50 PedMIDAS scores).

Figure 3.7.7
A histogram to show the distribution of the FIQ negative marker food scores according to the four migraine severity grades

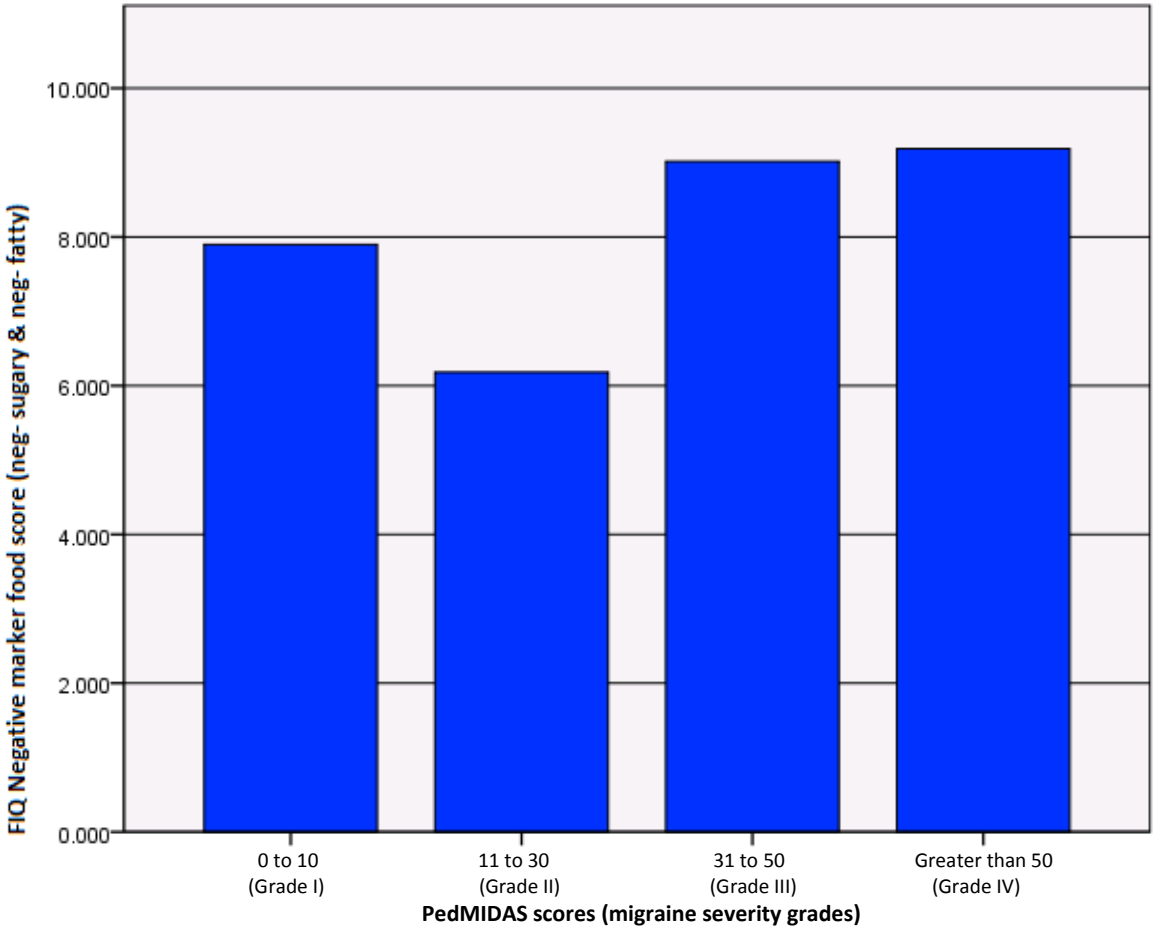


Figure 3.7.8
A histogram to show the distribution of the FIQ negative sugary food scores according to the four migraine severity grades

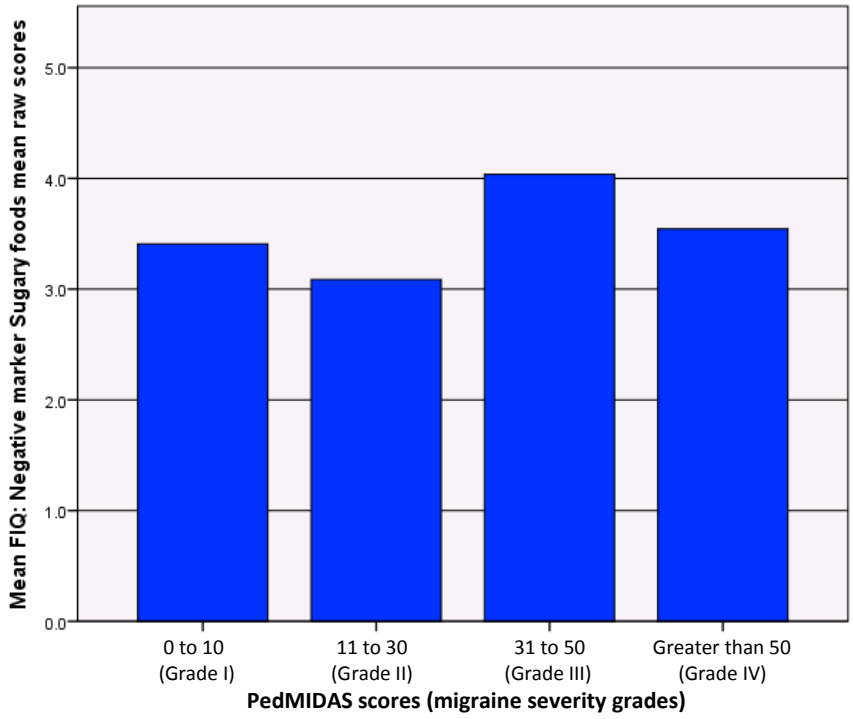


Figure 3.7.9
A histogram to show the distribution of the FIQ negative fatty food scores according to the four migraine severity grades

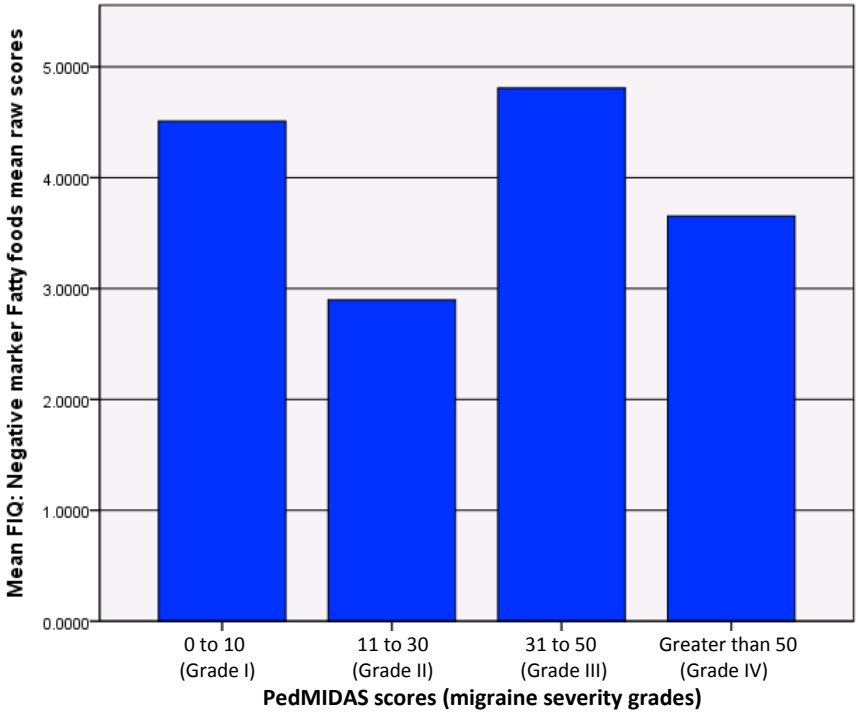


Figure 3.7.10
A histogram to show the distribution of the FIQ positive marker food scores according to the four migraine severity grades

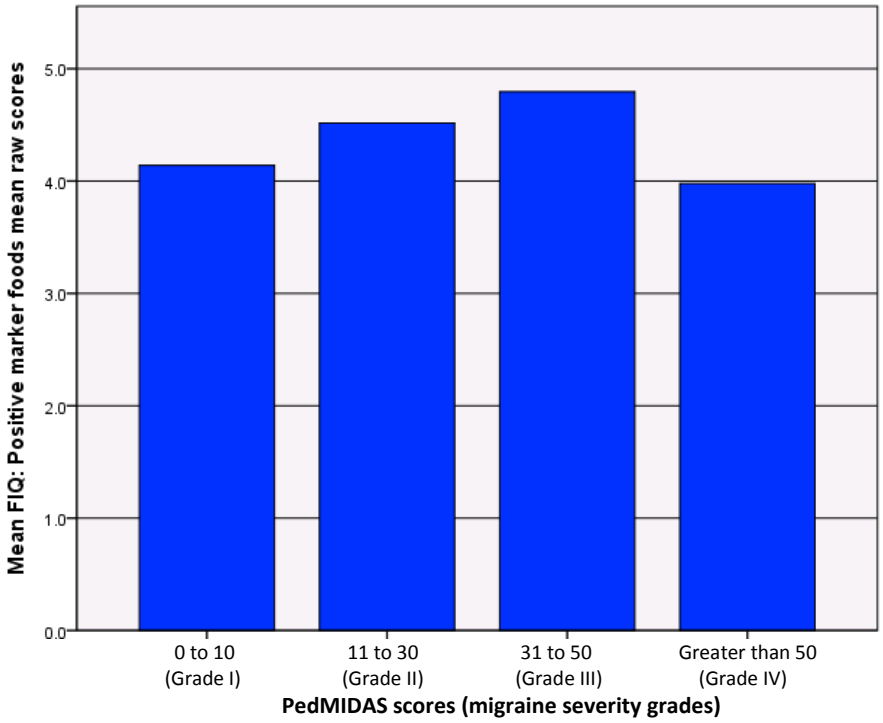


Figure 3.7.11
A histogram to show the distribution of the FIQ positive high fibre food scores according to the four migraine severity grades

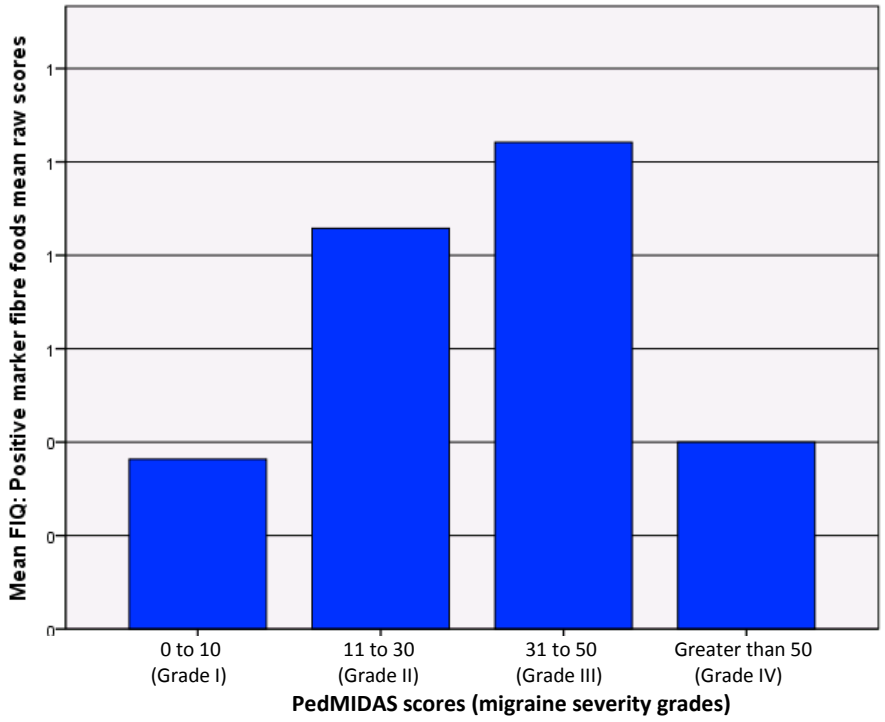


Figure 3.7.12
A histogram to show the distribution of the FIQ negative marker food scores according to the three monthly headache frequency groups

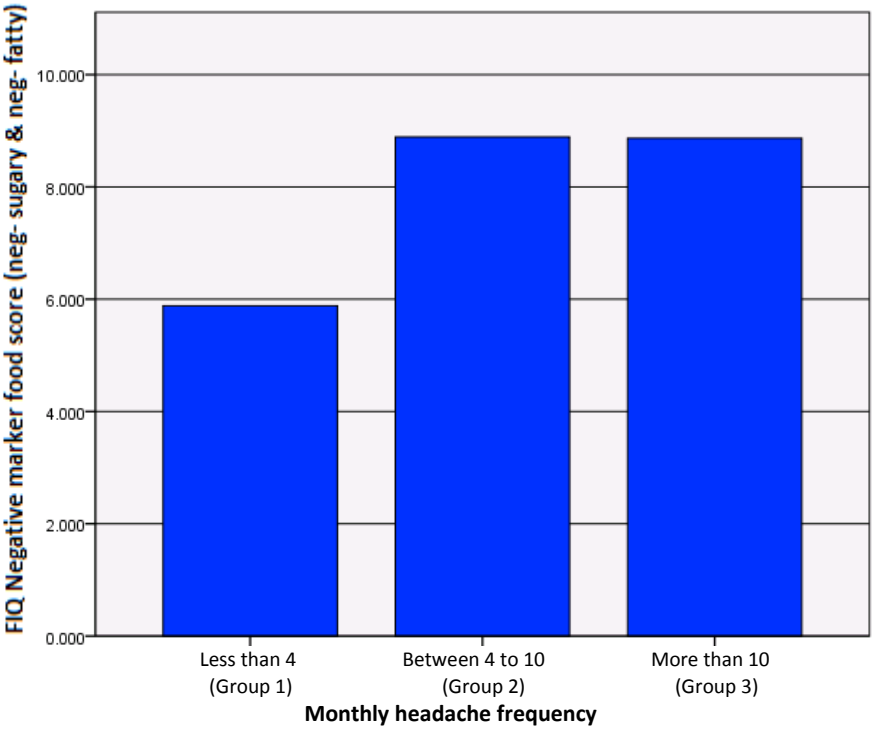


Figure 3.7.13
A histogram to show the distribution of the FIQ negative sugary food scores according to the three monthly headache frequency groups

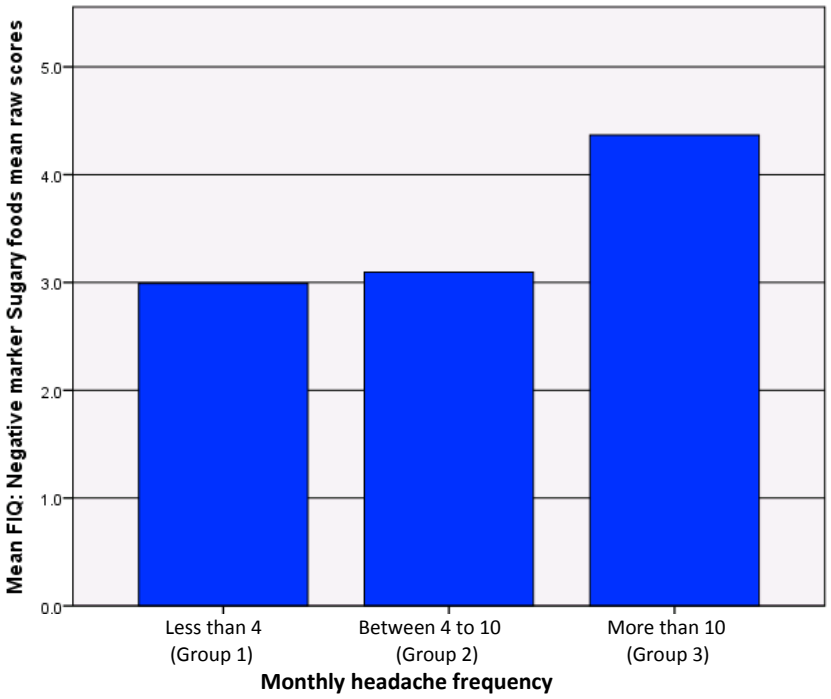


Figure 3.7.14
A histogram to show the distribution of the FIQ negative fatty food scores according to the three monthly headache frequency groups

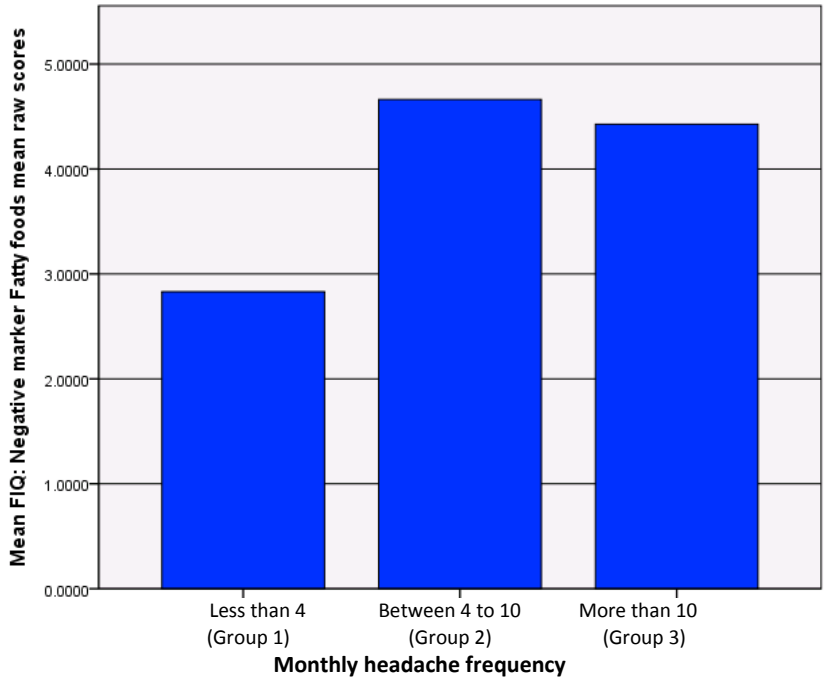


Figure 3.7.15
A histogram to show the distribution of the FIQ positive marker food scores according to the three monthly headache frequency groups

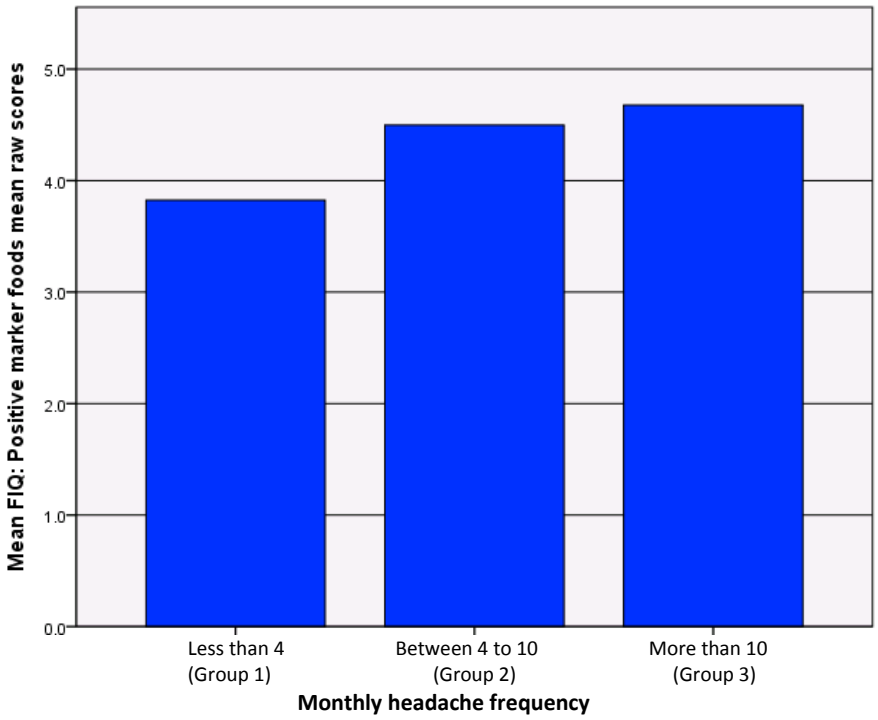
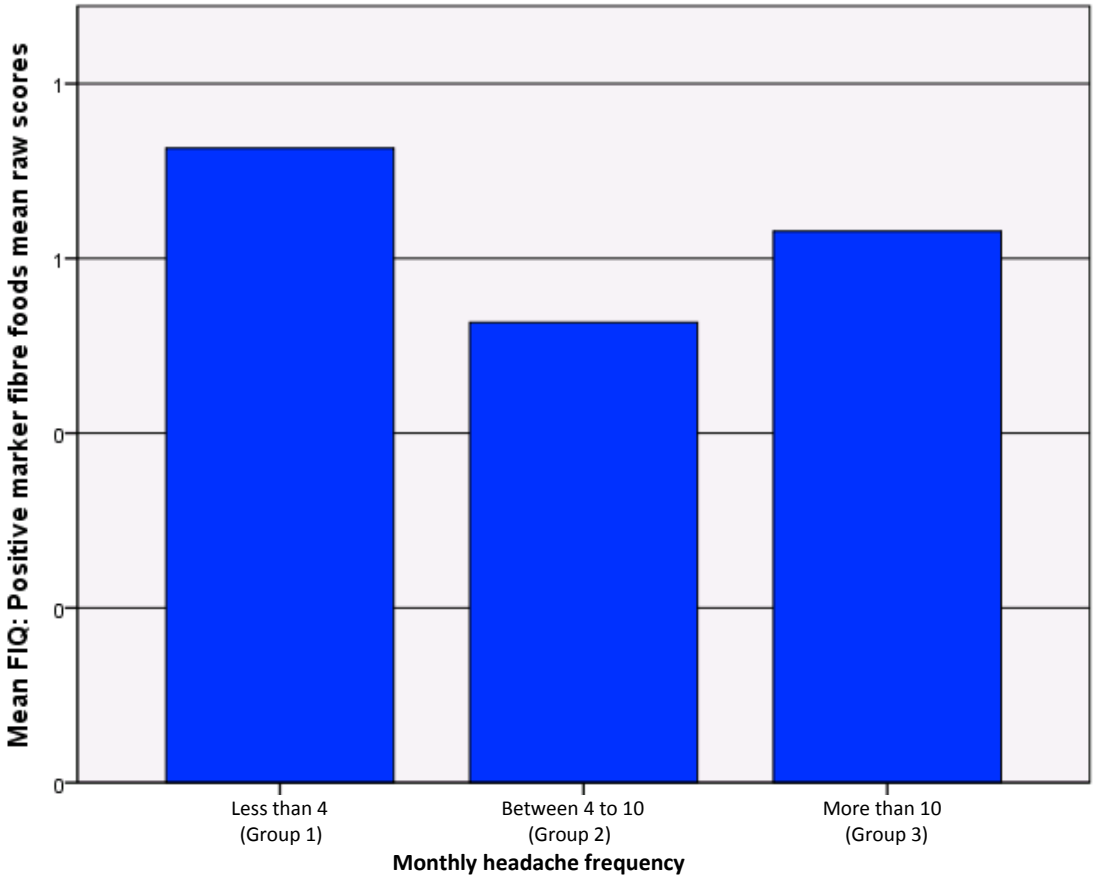


Figure 3.7.16
A histogram to show the distribution of the FIQ positive high fibre food scores according to the three monthly headache frequency groups



Comparison of the FIQ subscale scores between the four migraine severity grades

As outlined by table 3.7.6, when the FIQ data was compared between the four migraine severity grades, the chi-square value for each FIQ subscale was insignificant at the corrected probability level of 0.005. For this reason the hypothesis of "the FIQ subscale scores (neg- marker, neg- sugary foods, neg- fatty foods, pos+ marker and pos+ high fibre foods) will significantly ($p \leq 0.005$) differ between the four migraine severity grades" was rejected.

Comparison of FIQ subscale scores between the three monthly headache frequency groups

Based on the uncorrected p-value of 0.05, there were significant chi-square values for the comparison of negative marker food scores (chi-square= 5.95, p= 0.05), negative sugary food scores (chi-square= 6.76, p= 0.03) and negative fatty food scores (chi-square= 6.06, p= 0.05), between the three monthly headache frequency groups. However based on the corrected probability level of 0.005, there were no significant chi-square values for any of the FIQ subscales. So based on the latter evidence the hypothesis of "the FIQ subscale scores (neg- marker, neg- sugary foods, neg- fatty foods, pos+ marker and pos+ high fibre foods) will significantly (p≤ 0.005) differ between the three monthly headache frequency groups" was rejected.

FIQ Subscale	PedMIDAS Migraine severity grades Chi-square value (p-value)	Monthly Headache Frequency categories Chi-square (p-value)
Neg- marker foods	2.39 (0.50)	5.95 (0.05)
Neg- marker sugary foods	0.93 (0.82)	6.76 (0.03)
Neg- marker fatty foods	4.67 (0.20)	6.06 (0.05)
Pos+ marker foods	0.81 (0.85)	1.72 (0.42)
Pos+ marker fibre foods	6.82 (0.08)	1.52 (0.47)

Table 3.7.6- Kruskal-Wallis test results for the comparison of FIQ subscale scores between the migraine groups

Food Intake Questionnaire (FIQ) and Child behaviour Checklist Correlations

As outlined in table 3.7.7, none of the FIQ subscales were significantly (p≤ 0.05) correlated with any of the CBCL subscale T-scores. For this reason the hypothesis of "the FIQ negative marker, negative sugary and negative fatty food scores will have a significantly (p≤ 0.05) positive correlation with the CBCL subscale (internalising/ externalising/ total) T-scores" was rejected. The hypothesis of "the FIQ positive marker and positive high fibre foods scores will have a significantly (p≤ 0.05) negative correlation with CBCL subscale (internalising/ externalising/ total) T-scores" was also rejected.

FIQ Sub scale	CBCL Externalised T-scores r_s value (p-value)	CBCL Internalised T-scores r_s value (p-value)	CBCL Total T-scores r_s value (p-value)
Negative marker foods	0.14 (0.30)	0.13 (0.34)	0.16 (0.22)
Negative marker Sugary foods	0.15 (0.24)	0.22 (0.09)	0.21 (0.18)
Negative Fatty foods	0.19 (0.14)	0.09 (0.50)	0.17 (0.20)
Positive marker foods	-0.21 (0.11)	-0.01 (0.96)	-0.15 (0.25)
Positive fibre foods	0.15 (0.26)	0.02 (0.86)	0.07 (0.62)

Table 3.7.7- Spearman rank correlation results between the FIQ subscale scores and CBCL subscale T-scores

Chapter 3.8

Child Behaviour Checklist (CBCL) results

Distribution CBCL T-scores

Raw scores produced from each subscale (internalising/externalising/total) of the Child Behaviour Checklist (CBCL) were converted to T-scores that were adjusted for age and sex. The reference range scores used to convert the raw scores to standardised T-scores were obtained from the CBCL Achenbach manual[213].

The histograms for the distribution of T-scores for each CBCL subscale, in figures 3.8.1 to 3.8.3, display a non-skewed appearance. This is in keeping with the fact that the data for all three CBCL subscales were of a parametric distribution.

Figure 3.8.1- A histogram to display the distribution of externalised CBCL T-scores

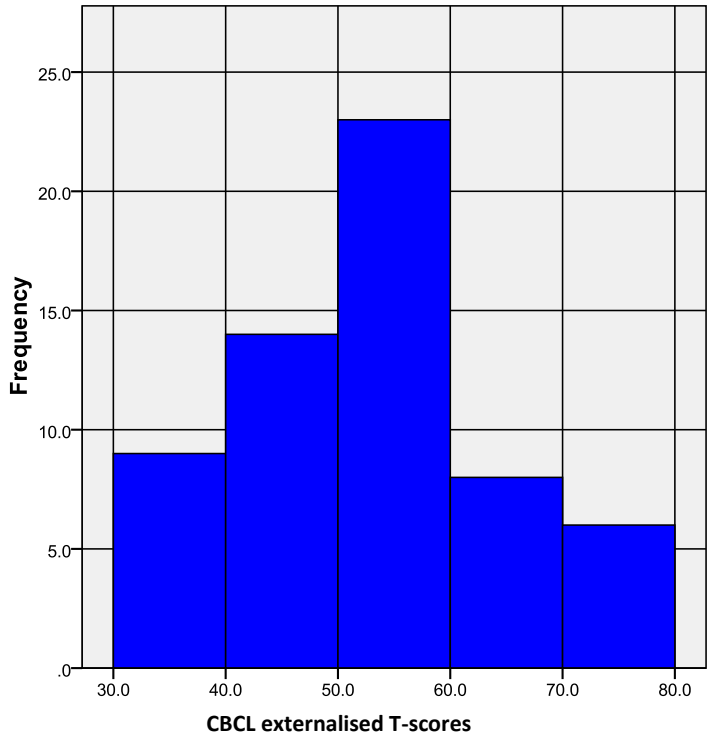


Figure 3.8.2- A histogram to display the distribution of internalised CBCL T-scores

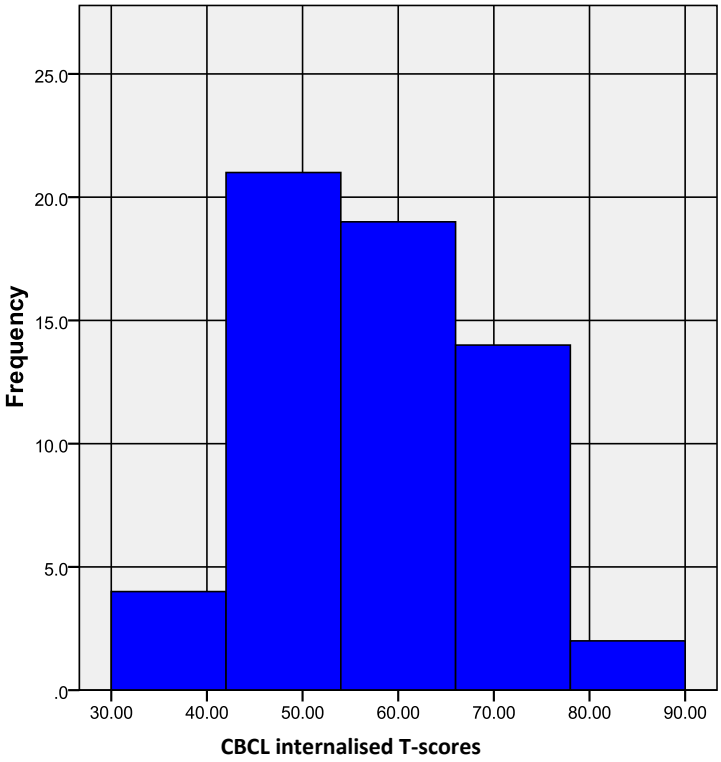
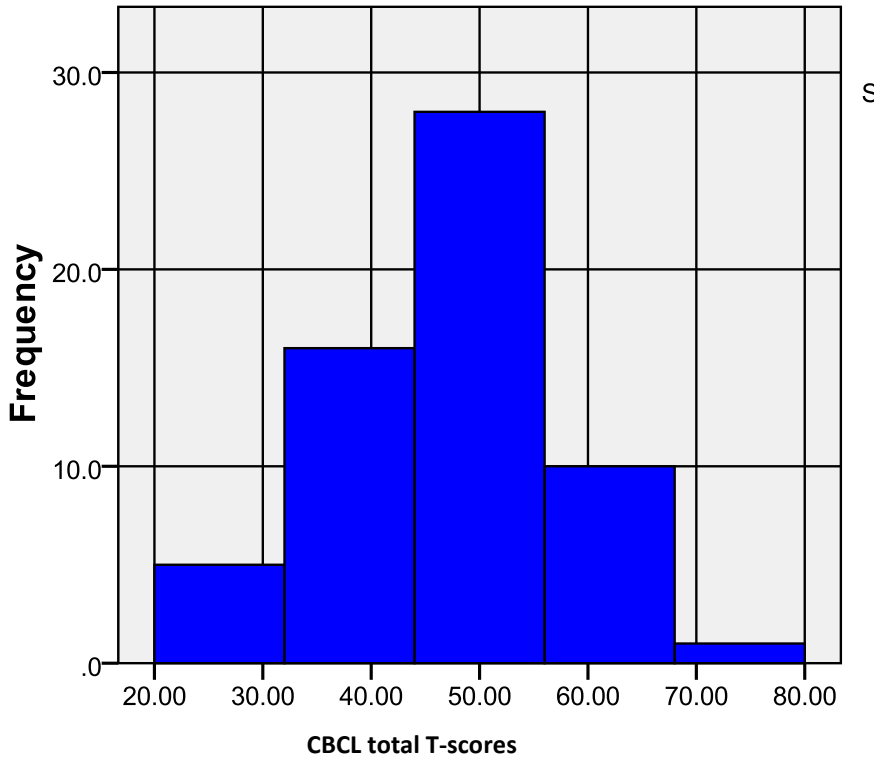


Figure 3.8.3- A histogram to display the distribution of total CBCL T-scores



Distribution	Internalising	Externalising	Total
Mean (s.d)	57 (11)	52 (12)	47 (11)
Median	58	53	48
Mode	53	50	34
Minimum	33	33	24
Maximum	86	75	72

Table 3.8.1- Distribution of CBCL T-scores

The overall mean T-score for the entire study sample (n= 60) was calculated for each CBCL subscale, which can be seen in table 3.8.1. The mean T-scores for the internalising (mean= 57, median = 58), externalising (mean= 52, median= 53) and total (mean= 47, median= 48) CBCL subscales were very similar to the respective median values. The internalising subscale showed the largest difference between the minimum and maximum T-scores reported (minimum value= 33; maximum value= 86).

Subscale CBCL T-scores according to reference ranges

The frequencies of patients with CBCL T-scores within the normal, sub clinical and clinical ranges have been plotted as histograms which can be seen in figures 3.8.4 to 3.8.6. The cut-off limits used to assess the clinical status of CBCL scores (as outlined in tables 3.8.2 and 3.8.3) were derived from the Achenbach manual[213].

As can be seen in figure 3.8.4, the majority of patients have an externalising CBCL T-score within the normal range profile (n= 46, 77%). As shown in figure 3.8.5, there was a higher percentage of patients with internalising T-scores in the clinical range (n= 23, 38.3%) compared with the percentage of patients with externalised T-scores in the clinical range (n= 12, 20%). Figure 3.8.6 illustrates that the majority of patients had total CBCL T-score within the normal (non-clinical) profile.

CBCL Scale	Normal	Sub-clinical	Clinical
Internalising	0-10	11 - 13	14-64
Externalising	0-11	12 - 15	16-70
Total	0-35	36 - 44	45-134

Table 3.8.2- Normal/sub-clinical/clinical cut off limits for CBCL T-scores in Girls

CBCL Scale	Normal	Sub-clinical	Clinical
Internalising	0- 8	9 -11	12- 64
Externalising	0- 11	12 – 15	16- 70
Total	0- 39	40- 51	52- 134

Table 3.8.3- Normal/sub-clinical/clinical cut off limits for CBCL T-scores in Boys

Figure 3.8.4
A histogram to show the frequency of patients with an externalising CBCL T-score within the normal, clinical and sub-clinical ranges

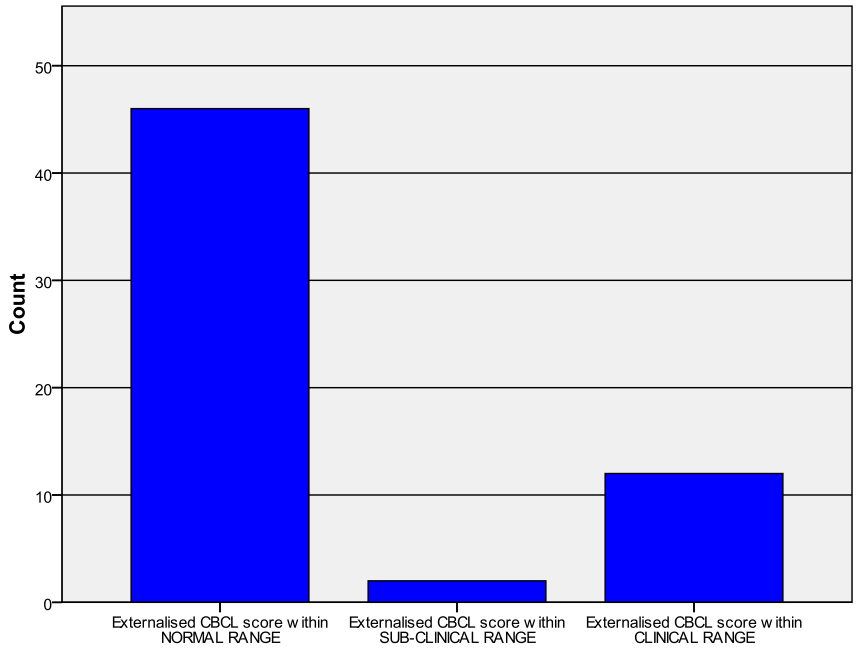


Figure 3.8.5
A histogram to show the frequency of patients with an internalising CBCL T-score within the normal, clinical and sub-clinical ranges

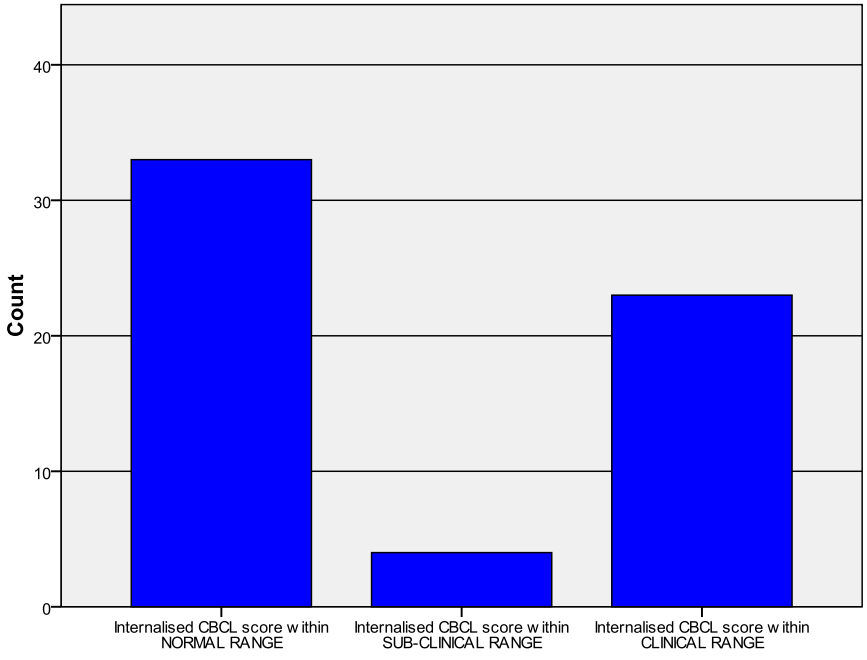
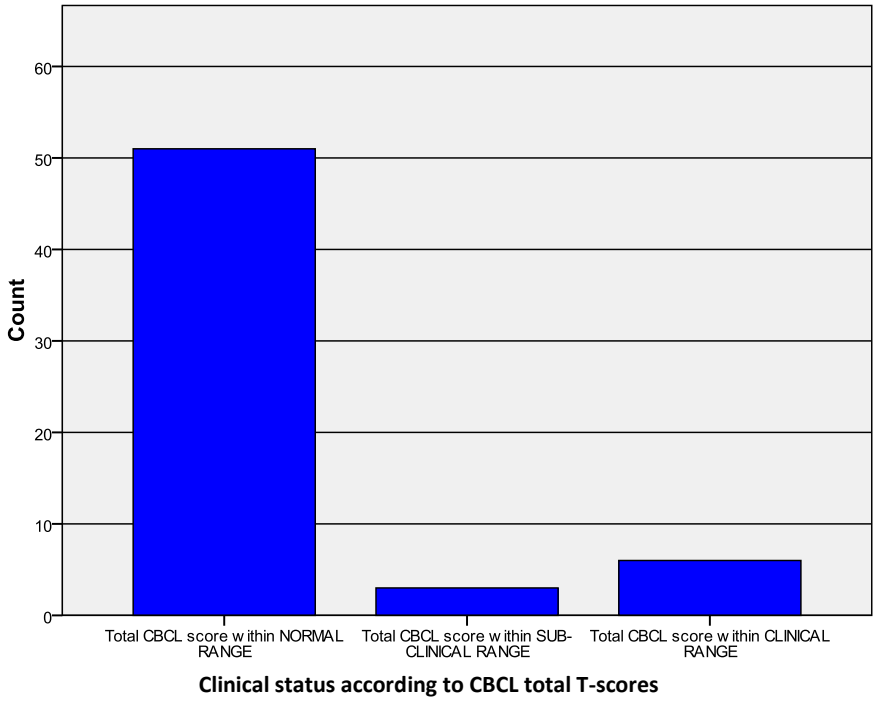


Figure 3.8.6
A histogram to show the frequency of patients with a total CBCL T-score within the normal, clinical and sub-clinical ranges



CBCL T-score Correlations with the PedMIDAS scores and monthly headache frequency

Spearman's rank correlation test was used to assess the correlations between the CBCL subscales and PedMIDAS / monthly headache frequency. This was done on the basis that the data set for PedMIDAS scores was of a non-parametric distribution.

As outlined in table 3.8.4, there were no significant ($p \leq 0.05$) correlations between any of the CBCL subscale T-scores and the monthly headache frequency values. For this reason the hypothesis of "the subscale CBCL T-scores will have a significantly ($p \leq 0.05$) positive correlation with the monthly headache frequency values" was rejected.

The internalising CBCL subscale (r_s= 0.35, p= 0.01) and total CBCL subscale (r_s= 0.27, p= 0.04) each had a weak but significantly (p≤ 0.05) positive correlation with the PedMIDAS scores. For this reason the hypothesis of "the internalising CBCL T-scores and the total CBCL T-scores will have a significantly (p≤ 0.05) positive correlation with the PedMIDAS scores" was accepted.

As outlined by table 3.8.4, the externalising T-scores were not significantly (p≤ 0.05) correlated with the PedMIDAS scores. For this reason the hypothesis of "the externalising CBCL T-scores will have a significantly (p≤ 0.05) positive correlation with the PedMIDAS scores" was rejected.

CBCL Category	PedMIDAS raw scores r_s (p value)	Monthly Headache Frequency r_s (p value)
Externalised	0.20 (0.12)	0.02 (0.87)
Internalised	0.35* (0.01)	0.07 (0.62)
Total	0.27* (0.04)	0.09 (0.48)

Table 3.8.4- Spearman rank correlation results between CBCL subscale T-scores and migraine measures. *= significant finding (p ≤0.05)

CBCL T-score Correlations with BMI z-scores

Given that the data for the BMI z-scores and every CBCL subscale followed a parametric distribution, the correlations between the BMI z-scores and the CBCL subscale T-scores were assessed using the parametric Pearson's correlation test.

As can be seen from table 3.8.5, the internalising CBCL T-scores (r= 0.28, p= 0.03) and the total T-scores (r= 0.28, p= 0.03) both had a significantly (p≤ 0.05) positive correlation with the BMI z-scores. For this reason the hypothesis of "the BMI z-scores will have a significantly (p≤ 0.05) positive correlation with the CBCL internalising T-scores and the CBCL total T-scores" was accepted.

As outlined in table 3.8.5, the externalising T-scores did not have a significantly (p≤ 0.05) positive correlation with the BMI z-scores (r =0.17, p= 0.18). For this reason the hypothesis of "the BMI z-scores will have a significantly (p≤ 0.05) positive correlation with the CBCL externalising T-scores" was rejected.

CBCL subscale	BMI z-scores r (p-value)
Externalised Behaviours T-scores	0.17 (0.18)
Internalised Behaviours T-scores	0.28 (0.03)*
Total T-scores	0.28 (0.03)*

Table 3.8.5- Pearson's correlation test results for the correlation between BMI z-scores and CBCL subscale T-scores. *= significant finding (p ≤0.05)

Chapter 3.9

Overview of study results and their possible implications

Significant findings	Implication of result
Desire to drink (DD) positively correlated with PedMIDAS raw scores (r_s= 0.41, p= 0.01)	Desire to drink is positively associated with migraine severity
FIQ negative marker foods significantly positively correlated with monthly headache frequency (r_s= 0.27, p= 0.04)	Intake of negative unhealthy foods is positively associated with monthly headache frequency
Significant correlation between PedMIDAS scores and internalised CBCL T-scores (r_s = 0.35, p= 0.01)	Internalising behavioural problems are positively associated with migraine severity
Significant correlation between PedMIDAS scores and Total CBCL T-scores (r_s= 0.27 , p= 0.04)	Overall Behavioural problems are associated with migraine severity
Significant correlation between BMI z-scores and internalised CBCL T-scores (r = 0.28, p= 0.03)	Internalising behavioural problems are associated adiposity
Significant correlations between BMI z-scores and total T-scores (r = 0.28, p= 0.03)	Overall behavioural problems are associated with adiposity

Table 3.51- List of significant study findings

Chapter 4.0- Discussion

Chapter 4.1

Desire to drink and Migraine Severity

The desire to drink subscale of the CEBQ had a significantly ($p \leq 0.05$) positive correlation with the PedMIDAS scores ($r_s = 0.41$, $p = 0.01$); as the PedMIDAS scores were used as a proxy for migraines severity this finding indicated children with higher severities of migraine have a greater desire to consume fluids.

During acute migraine attacks there is a substantial rise in urine volume and reduction in excretion of urinary arginine vasopressin (AVP) due to the inhibition of AVP secretion from the hypothalamus. Hypothalamic activity is linked with cortical spreading depression, which may cause inhibition of neurotransmission along the supra-optic nucleus with consequent impairment of vasopressin secretion[214,215]. Dehydration is accepted as a potential trigger for headache attacks in some migraine patients. Increased water consumption given as preventive migraine therapy is associated with 21 hours worth of fewer headaches suffered compared with patients not given hydration treatment[216]. It can be purported that the significantly positive correlation observed between the desire to drink fluids and migraine severity (as measured by the PedMIDAS scores) was due to children with greater severities of migraine consuming larger amounts of fluids in aid to alleviate their headache pain.

Hypothalamic dysfunction is associated with a lack of thirst perception. Osmoreceptors responsible for osmometric thirst are located in the anterior hypothalamus. Hypertonic injections of saline solutions into the hypothalamus are demonstrated to induce states of thirst[217]. PET scanning has shown there is increased hypothalamic activity during acute migraine attacks[125]. Given these findings it is possible that migraine patients express higher intensities of thirst through the mediating effects of hypothalamic osmo-regulation.

This pilot study did not detect a significant correlation between the CEBQ desire to drink subscale and BMI z-scores. However a previous study by Wardle et al has demonstrated a significant positive association between the CEBQ desire to drink subscale and BMI z-scores[218]. In children, the consumption of high sugar containing drinks is associated with increased BMI levels and high obesity risk. [219]. Children with a greater desire to drink may consume high calorie fluids which adversely increase adiposity levels. However it may be that the children in this pilot study with high desire to drink scores were not consuming high calorie drinks and hence also did not have high adiposity levels.

The Food Intake Questionnaire (FIQ) could have been used to qualitatively assess what types of drinks were consumed by children in this pilot study. The frequency of patients that consumed high or low calorie drinks could have been assessed for associations with migraine severity (as measured by the PedMIDAS scores) and the desire to drink subscale of the CEBQ. However due to time constraints this analysis was not possible. Hence for the main future study it would be beneficial to analyse the relationship between fluid intake and migraine severity.

The statistician involved in this pilot study advised that a correlation coefficient of 0.70 or larger indicates the presence of a strong correlative relationship; hence it must be noted that the correlation coefficient between the CEBQ desire to drink scores and PedMIDAS scores was very small (r_s= 0.41), indicating a weak correlation. There was no supporting evidence that the CEBQ desire to drink z-scores significantly ($p<0.003$) differed between the four grades of migraine severity. A strong conclusion cannot be drawn from the results in this pilot study because of the very low power in sample size and high number of multiple tests. Hence based on results from this pilot study it can be concluded that there was a weak correlation between the desire to drink as measured by the CEBQ and migraine severity as measured by the PedMIDAS scores. A higher powered sample size would be needed to more accurately test the strength and significance of this relationship.

Chapter 4.2

Food intake and Monthly Headache Frequency

The Food Intake Questionnaire (FIQ) negative marker food scores had a significantly ($p \leq 0.05$) positive correlation with the monthly headache frequency ($r_s = 0.27$, $p = 0.04$). Given that the negative marker foods listed in the FIQ represented unhealthy foods high in sugar and fat[174], it can be suggested that migraine patients with higher headache frequencies consume more unhealthy food items listed in the FIQ in one day.

Although no significant findings for food cravings were observed in this pilot study, there is evidence of migraine patients suffering from cravings for chocolate, cheese and dry starchy foods during acute attacks[91]; these food items were also listed in the FIQ negative marker food subscale[174]. The foods consumed by migraine patients in this pilot study may have largely been a result of a hedonistic drive. Activation of the reward system as regulated by the hypothalamus and 5-HT neurotransmitters increase the ingestion palatable foods high in fat and simple sugars[220,221]. Hypothalamic activation, dopamine and serotonin dysfunction are associated with migraine pathology[222]. It is possible that children with migraine eat high fat sugary foods because of an increased activation of the reward system that is influenced by migraine associated pathological processes involving hypothalamic activation and serotonin dysfunction.

In this pilot study, 39 (65%) of the 60 patients that were recruited suffered from anorexia as an associated feature of their acute migraine attacks. Thus in consideration of acute migraine attacks representing states of appetitive loss, the significant positive correlation between monthly headache frequency and the intake of unhealthy (FIQ negative marker) foods could indicate that the unhealthy foods were consumed inter-ictally as part of the chronic “trait” form of migraine. However it must be noted that the results from the FIQ reflected dietary habits over a period of one day (i.e. the previous day to when the child was recruited into the pilot study). Hence for this reason it would not be possible to conclude

whether the relationship that the FIQ negative marker data had with monthly headache frequency was based on a chronic interaction between diet and migraine.

Headaches can develop in response to the consumption of cheese products that result in abnormal tyramine concentrations[223]. Chocolate can act as a trigger for headache onset in some migraine patients due to the release of phenylethylamine, caffeine and catechin, which can alter cerebral blood flow[224]. Fatty acids are speculated to be involved in migraine mechanisms as suggested by raised serum levels of free fatty acids and blood lipids during acute attacks[225]. Given that chocolate, cheese and caffeine products were listed as food items under the FIQ negative marker subscale[174], its relationship with headache frequency may be through mediating roles as a headache trigger; hence one possibility is that the greater ingestion of high fat sugary foods may have provoked more frequent migraine attacks. However given that this pilot study did not investigate food intake in relation to the acute onset of migraine attacks, it is not possible to form a conclusion about the role of negative marker ("unhealthy foods") as a migraine trigger. Instead this particular issue would require further research, with the use of a more robust dietary measure that is able to assess regular food intake for a time period that is longer than one day (i.e. not the FIQ).

The statistician involved in this pilot study advised that a correlation coefficient of 0.70 or larger indicates the presence of a strong correlative relationship; hence it must be noted that the correlation coefficient between the FIQ negative marker food scores and monthly headache frequency was very small (r_s= 0.27), indicating a weak correlation. There was no supporting evidence that the FIQ negative marker food scores significantly ($p<0.005$) differed between the three monthly headache frequency groups. A strong conclusion cannot be drawn from the results in this pilot study because of the very low power in sample size and high number of multiple tests. Hence based on results from this pilot study it can be concluded that there was a weak correlation between the intake of unhealthy "negative marker foods" as measured by the FIQ and monthly headache frequency. A higher powered sample size would be needed to more accurately test the strength and significance of this relationship.

Chapter 4.3

Behavioural problems, Migraine and Adiposity

The internalising CBCL T-scores had a significantly ($p \leq 0.05$) positive correlation with the PedMIDAS scores ($r_s = 0.35$, $p = 0.01$). However because the correlation coefficient was below the level of 0.70, it was considered a weak correlation. The total CBCL T-scores had a significantly ($p \leq 0.05$) positive correlation with the PedMIDAS scores ($r_s = 0.266$, $p = 0.04$). However because the correlation coefficient was below the level of 0.70, it was considered a weak correlation.

Sixty-nine different correlation tests were performed with the CBCL measure (23 for each CBCL subscale), see table 4.3.1. Hence according to the Bonferroni test the corrected p-value for correlations made with the CBCL would have been equal to 0.00072 (0.05/69=0.00072). Total CBCL T-scores and internalising CBCL subscale T-scores were not significantly correlated with PedMIDAS scores at the corrected probability level of 0.00072. Hershey et al found that internalising CBCL scores were higher among migraine patients compared with controls[126]. Although this pilot study had a very low power in sample size, it can be concluded that in support of Hershey et al[126], behavioural problems as measured by the CBCL were weakly correlated with migraine severity as measured by the PedMIDAS. However a higher powered sample size would be needed to more accurately test the strength and significance of this relationship.

The internalising CBCL T-scores had a significantly positive correlation with the BMI z-scores ($r = 0.276$, $p = 0.03$). However because the correlation coefficient was below the level of 0.70, it was considered a weak correlation. The total CBCL T-scores had a significantly positive correlation with the BMI z-scores ($r = 0.28$, $p = 0.029$). However because the correlation coefficient was below the level of 0.70, it was considered a weak correlation. It must be noted that at the corrected probability level of 0.00072, neither the internalising nor total

CBCL subscale T-scores were significantly correlated with the BMI z-scores. Vila et al[127] found obese children had higher levels of internalising behaviour problems compared with normal weight controls. Although this pilot study had a very low power in sample size, it can be concluded that in support of Villa et al[127], behavioural problems as measured by the CBCL were weakly correlated with adiposity as measured by the BMI z-scores. However a higher powered sample size would be needed to more accurately test the strength and significance of this relationship.

Variable/measure	Number of subscales for each variable/measure	Number of CBCL correlations made with each subscale	Total number of CBCL correlations made with each variable/measure
Migraine measures	2	3	6
DEBQ	3	3	9
CEBQ	8	3	24
FIQ	5	3	15
FCI-II	4	3	12
BMI z-scores	1	3	3
TOTAL			69

Table 4.3.1- The number of correlation tests performed with the CBCL tool

Chapter 4.4

Eating behaviours and Migraine

With the exception of the CEBQ desire to drink subscale, none of the eating behaviour subscales (as measured by the DEBQ for adolescents, DEBQ-C and CEBQ) were significantly ($p \leq 0.05$) correlated with migraine severity (as measured by the PedMIDAS scores) or monthly headache frequency. The eating behaviours did not significantly ($p \leq 0.008$ for the DEBQ results and $p \leq 0.003$ for the CEBQ results) differ according to the four migraine severity grades or three monthly headache frequency groups. Possible reasons for why these results were insignificant are now discussed.

Puberty as a confounding factor

This pilot study recruited a wide age range of children at different stages of pubertal development. Teenage girls can develop suppressed appetite levels in relation to cyclic peri-ovulatory oestradiol secretion. Testosterone can increase appetite levels by increasing meal frequency.[226]. Menstrual migraine related to abrupt falls in serum oestradiol concentrations is responsive to oestrogen replacement therapy. Oral contraceptive pills worsen migraine attacks in up to 55% of cases. Migraine symptoms can improve during pregnancy and after menopause[227]. This suggests there can be some oestrogen driven pathology among female migraine patients. Leptin levels that suppress appetite can increase in girls and decrease in boys after Tanner stage 2, when pubertal development proceeds[228]. Hence individual differences in pubertal developmental that affect oestrogen and leptin physiology[228,229] may have significantly confounded the migraine-eating behaviour relationship. To overcome this issue in the main future study it may be useful to assess the stage of pubertal development of each child recruited. The Tanner scale is widely accepted as a face valid criterion for assessing stages of pubertal development. It grades the stage of pubertal development according to pubic hair distributions and genital maturation (breast growth in girls and testicular/penis growth in boys)[229]. However by implementing the Tanner scale the ethics approval of the main future study would have to be severely revised due to the disclosure of highly sensitive information on genital anatomy.

Emotional eating and migraines

The theory of emotional eating posits that excessive food consumption occurs in response to high emotional arousal which in the long term increases adiposity levels[70]. However the threshold for emotional arousal that stimulates over-eating has not been outlined in the eating behaviour literature[71]. Migraine cases in this pilot study were quite emotionally stable based on the Child Behaviour Checklist T-scores. Of the total 60 patients 51 subjects (85%) displayed normal behavioural traits and only 6 children (10%) had behavioural

problems within the clinical range. Given that 85% of the child recruits displayed normal behavioural tendencies, they may also be quite emotionally stable, meaning they were not able to reach a certain threshold of consistent emotional arousal[72] needed to induce states of emotional eating.

Restrained eating and migraine

Pre-pubertal children often report a heightened sense of body dissatisfaction and may begin dieting from as young as 9 years old[209]. Restrained eating is the abandonment of the usual cognitive resolve to diet caused by states of dis-inhibition[72]. Particular triggers for dis-inhibition such as alcohol consumption are not present in early childhood as well as other possible triggers such as emotional instability. Thus it is possible that restrained eating levels were normal in the younger children recruited. There is no current literature that outlines the minimum age in which high restrained eating levels can develop[73]. This issue must be taken into consideration as it may account for why there was no significant relationship detected between migraines and restrained eating.

External eating and migraines

Strict parental control on diet can motivate rule breaking behaviour in children which encourages them to consume foods not usually accepted by parents. Up to 61% of families with children under the age of 18 have parents that both work and 72% of single parents that work full time[230]. If parents are busy with employment responsibilities, children have a greater freedom in dietary food choices. Hence children do not have to oppose strict parental rules on diet and do not develop rule breaking behaviour[81]. It may be that patients recruited into this study did not respond to externalised food cues as readily, due to a lack of urge for breaking strict parental rules on diet.

CEBQ and migraines

Food responsiveness, enjoyment of food, satiety responsiveness, speeds of eating, food fussiness and emotional over/under eating are all subject to food hedonism as a factored determinant[60]. High levels of food responsiveness and enjoyment of eating are both associated with strong levels of hedonism for high fat foods. The consumption of highly palatable foods is associated with slow eating speeds to savour food flavours[231].

Emotional instability leads to the consumption of highly palatable foods that provide comfort, indicating emotional eating has a hedonistic eating component. Food hedonism is influenced by foods available in the environment, social factors, somato-psychic state, subjective experiences and preparatory activities[232]. As none of these factors were accounted for in this pilot study it is possible they may have affected eating behaviours measured by the CEBQ.

Children with social companionship whilst eating tend to develop a larger appetite and eat larger food servings. Children told “not to leave food on their plate when finished eating”, are less sensitive to physiological satiety cues[234]. Strict authoritarian parental feeding practices are associated with the consumption of “forbidden foods” even when satiated from a prior full meal[59]. Hence unaccounted factors such as familial eating practices and social interactions may have affected the eating behaviour results in this pilot study through mediating effects on hedonism[153].

The results in this pilot study suggest that eating behaviours were not associated with migraines. However a strong conclusion cannot be drawn from these results because of the very low power in sample size, high number of multiple tests, pubertal confounding factors and unaccounted factors that affect levels of food hedonism. A future study is needed to test the relationship between migraines and eating behaviours based on a much larger sample size.

Chapter 4.5

Migraine and Adiposity

In this pilot study, BMI z-scores were not significantly ($p \leq 0.05$) correlated with the PedMIDAS scores (migraine severity) or monthly headache frequency. BMI z-scores also did not significantly ($p \leq 0.025$) differ between the four migraine severity grades or between the three monthly headache frequency groups. Possible reasons for why these results were insignificant are now discussed.

Migraine is controlled by a complex interaction between genetic and environmental determinants[233]. Parental weight is positively correlated with the body mass index of their children and is a predictor of childhood obesity. Children with at least one overweight parent have a 3 fold risk of becoming overweight and children with an obese parent have a 5 fold risk of becoming overweight[107]. The FTO gene is strongly associated with obesity[108]. FTO mRNA highly expressed within regulatory appetite centres of the hypothalamus, increase adipose fat levels and lower lean mass by desensitising responses to internal satiety cues and increasing appetite. No specific common gene with shared effects on migraine and adiposity has yet been identified[109]. However migraine, eating behaviours and adiposity are each influenced by genetic traits[104] that may have affected the migraine-adiposity relationship tested in this pilot study.

Based on large population samples, body mass index is a validated measure of adiposity across the age of 2 to 18 years[234]. However BMI is an indirect measure of adiposity and has not yet been validated in small sample size studies[235]. Hence BMI z-scores in this pilot study may not have accurately reflected adiposity levels because of the very small sample size. To resolve this issue for the main future study a much larger sample size would need to be recruited. Alternatively adiposity could be measured using a different measurement technique.

As all of the patients recruited into this pilot study were approached at their first clinic visit, the severity of their migraine illness may have been in the early stages of progression as the underlying pathology may not have reached its full potential. Migraine progression is measured clinically by headache frequency, with the chronic form of migraine representing the more severe spectrum of migraine progression[1]. Only 6 of the patients recruited in this pilot study met the criteria for a chronic migraine diagnosis (greater than 15 monthly headaches) suggesting that 90% of the patients recruited still had potential to progress from an episodic to a chronic form of migraine[5]. Bigal et al identified a migraine-adiposity relationship based on chronic daily headache patients with a late progression of migraine[41]; this supports the possibility that migraine pathology has to reach a certain threshold before it is able to influence adiposity levels.

The results in this pilot suggest that BMI z-scores were not associated with migraine severity or headache frequency. However a firm conclusion cannot be drawn from these results based on unaccounted genetic influences, questionable validity of BMI as an adiposity measure in such a small sample size population and short length of study. Hence a future study is needed to test the relationship between migraines and adiposity based on a much larger sample size with adequate length of study period.

Chapter 4.6

Migraine and food cravings

None of the FCI-II subscale raw scores were significantly ($p \leq 0.05$) correlated with the PedMIDAS scores (migraine severity) or the monthly headache frequency values. FCI-II subscale raw scores did not significantly ($p \leq 0.006$) differ between the four migraine severity grades or three monthly headache frequency groups, indicating that food cravings were not associated with migraines. Previous studies have only reported food cravings during acute migraine attacks[146], and not in the chronic trait form of migraine as investigated in this pilot study. In addition to this the sample size was not adequately powered and so a firm conclusion cannot be made about the relationship between food cravings and migraines.

Chapter 4.7

Critical appraisal of questionnaires

Critical appraisal of the DEBQ for adolescents and the DEBQ-C

The Children's Dutch Eating Behaviour Questionnaire (DEBQ-C) presented some difficulties when used in the clinical field. Patients were frequently unable to grasp the meaning of some of the DEBQ-C questions. The recruiting researcher had to use familiar examples and create hypothetical scenarios to aid the child's understanding of the question. However by doing so the answer given may not have been face valid to the original question asked.

Both the DEBQ for adolescents and the DEBQ-C were subject to recall bias, especially with the emotional eating questions, that required a recollection of prior moments when emotional arousal induced states of hunger. Question 2 of the DEBQ-C ("if you feel depressed or lonely do you get a desire for food"), created problems as sometimes the child was unaware when they had previously felt depressed or lonely, and found it difficult to correlate such states of emotional arousal with feelings of hunger.

The 3-point answer scale in the DEBQ-C ("no", "sometimes" or "yes") was clear and appropriate to understand for children aged 7-12 years, causing no major problems. However some children found it difficult to use the 5-point answer scale in the DEBQ for adolescents ("never", "rarely", "sometimes", "often" or "always"). Some children were unsure of which option to choose, in the end stating "sometimes" as a neutral answer. This may have invalidated the DEBQ (for adolescents) results to a certain extent.

Patients found it difficult to report on some of the external eating questions such as "do you feel like eating when you walk past a snack bar?" This is because some children did not know whether food had to be consumed within a specific time frame from when exposed to the food cue.

Critical appraisal of the Child Eating Behaviour Questionnaire (CEBQ)

Parents were confused with the meaning of some of the statements used in the CEBQ. The first enjoyment of food statement ("my child loves food") made parents contemplate whether this meant the child likes to eat a lot or just enjoy eating all kinds of food. Many parents were very unsure about how to comment on the statement, "if given the choice my child would eat most of the time", as this is based on a hypothetical situation rather than an actual experience. Parents found it difficult to comment on item 35 ("my child eats more and more slowly throughout a meal") because this statement describes a progressive action that has to be carefully observed, which many parents had never done. It was difficult to comment on the statement, "my child eats more when annoyed/ anxious", because many children did not discuss whether they had feelings of angst or annoyance with their parents.

Critical appraisal of FCI-II

As food cravings are a hypothetical construct by definition and are not directly measurable. Thus inherent problems can arise in any tool measuring food cravings. The definition of a craving used by the food craving inventory (FCI-II) was “an intense desire to consume a particular food or food type that is difficult to resist”. Some children asked about how strong the desire must be to be defined as a craving, but because further details on this point were not delineated in the FCI-II tool the recruiting agent had to provide his own interpretation of the question. Many children found it difficult to distinguish the difference between a food craving and the actual consumption of food, especially in the younger age group below 10 years. As the FCI-II is an American based tool, certain food items listed were unfamiliar to English cuisine such as “corn bread” of the high fats subscale and “cinnamon rolls” of the sweets subscale. Thus for such food items the response was always “has never been craved”, which may have slightly invalidated craving results for the corresponding food groups. Children had to respond to a 5 point-scale with the options of “never”, “rarely”, “sometimes”, “often” and “always/ everyday”. Many children who were unsure of their day to day frequency of food cravings chose “sometimes” as a neutral answer, which may have invalidated results.

Critical appraisal of the Food Intake Questionnaire (FIQ)

The FIQ was subject to recall bias. Children found it difficult to recall whether certain foods were eaten the day before and many times the parent had to provide help. It is possible that the parent provided biased answers by overstating the consumption of healthy “positive marker” foods and understating the consumption of unhealthy “negative marker” foods. The FIQ has only been used in large sample size studies involving usually greater than 100 participants. This pilot study was the first to implement the FIQ tool in a small sample size with 60 patients. Hence the FIQ may not have been valid or reliable for use in this pilot study because its previous applications are based on large scale population samples.

Critical appraisal of the CBCL

The second chapter of the CBCL included questions on whether the child exhibited particular signs of behavioural dysfunction. Parents found some of the statements quite strange, such as “bowel movements outside the toilet”, and had to clarify their interpretation of the question. Some parents of young pre-adolescent boys were unable to comment on sexual statements such as “my child thinks about sex too much” or “my child suffers from sexual problems”, as this type of information was not usually disclosed to the parent.

Critical appraisal of the PedMIDAS tool

The PedMIDAS tool has been widely used in various headache studies and has been cited as a sensitive, reliable and valid measure of headache induced disability[185,188]. In terms of the practicalities of the PedMIDAS there were particular issues raised when used in the clinical field that requires discussion.

The PedMIDAS enquired about the number of days missed from daily social, school and domestic activities over the past 3 months. In the early recruitment stages from October 2009 to November 2009, children had not been at school long enough to report the number of headache related school absences in the past 3 months. Hence the PedMIDAS results produced from children during the early stages of recruitment may be under represented in contrast to those recruited after the November 2009 period.

The second PedMIDAS question asked about the number of headache related partial day school absences. How much of a school day that has to be missed in order to constitute a partial day absence was not stated in the PedMIDAS. Many children were sent home just before the end of a school day or arrived late. For these reasons many patients found it very difficult to answer question two. The recruiting agent had to make a decision to include all school days in which the expected number of hours attended in school was affected by headaches. However by doing so it is possible that the PedMIDAS scores were overestimated.

The third question asked “how many days did you function at less than half your ability in school due to headaches?” If school performance (i.e. ability to concentrate/focus in the classroom and complete work) was affected by headaches, it was difficult to quantify the reduction in functionality. Unable to do so, the presence of any headache associated functional deterioration was used as a marker for the number of school days the child functioned at less than half their ability. However by doing so the answers for question 3 may have been overstated.

Question four asked “how many days were you not able to do things at home (i.e. chores, homework, etc) due to a headache?” Many children were not accustomed to domestic chore work and were thus unable to provide valid response, because an answer of zero would not have been a true reflection of what was asked. Alternative activities such as reading and social networking were provided. However providing diverse examples of domestic activities may have jeopardised the construct validity of question four.

Question five (“how many days have you been unable to participate in other activities due to headaches?”) was found to be clear and well understood. Conversely, in question 6 (“how many days did you participate in these other activities but functioned at less than half your ability?”) it was again difficult to quantify functionality. All days where functional ability in “other activities” was affected by headaches were included in the answer.

The PedMIDAS required an apt memory of the number of activities affected by headaches in the last 3 months, and for this reason was highly subject to recall bias. On numerous occasions the child and parent would simply calculate the number of monthly absences and then multiply that by 3 to produce a rough estimated answer. Thus the answers provided were not always an accurate response to the questions asked.

Chapter 4.8

Adjustments for future study

In light of the limitations outlined in the previous discussion chapters there are certain adjustments and improvements recommended for the main future study on migraines, eating behaviours and adiposity, which will now be discussed.

Only 6 patients in this pilot study suffered from greater than 15 monthly headaches, indicating that chronic daily headache migraine patients were under-represented. Only 11 patients scored a PedMIDAS mark greater than 50 indicating severe migraines were also under-represented. Hence the under representation of severe and chronic daily headache migraine patients may have reduced the spectrum of migraine disease that was analysed in this pilot study. A wider range in disease spectrum that included a high representation of mild, moderate and severe migraine patients, may have allowed a more accurate assessment of correlation analyses with the eating behaviour and adiposity variables. For this reason it would be advisable to recruit a study sample that consists of similar proportions of mild, moderate and severe migraine severity, as well as similar proportions of chronic daily headache and episodic headache migraine patients. For this to happen, a larger sample of patients would need to be recruited.

The primary study objective to compare eating behaviours between migraine cases and non-migraine headache controls could not be fulfilled because an insufficient number of non-migraine control patients were recruited. As there was no comparison control group, the power to detect a significant relationship between eating behaviours and migraines was greatly reduced.

Previous studies that detected significant associations between migraines and adiposity were based on very large sample sizes[39-45]. Using such a small sample size in this pilot study reduced the power to detect any significant results which was a major limitation. Sixty patients was considered an appropriate sample size for the primary outcomes of this study

and was feasible for the 8 month recruitment phase. However for the main future study a larger sample size would be needed to increase the power of the study, calculations for which can be seen in table 4.8.1.

The minimum clinically important difference (MCID) required for sample size calculation was based on the restrained eating subscale of the Dutch Eating Behaviour Questionnaire for adolescents, because it is the most utilised and validated eating behaviour scale of the DEBQ (for adolescents)[73]. Although the level of restrained eating behaviour may be low in young children, it has been evidenced to be high among adolescents, particularly teenage girls[74].

As the future study would assess the relationship between migraines and eating behaviours, the MCID would be the minimum difference in restrained eating scores between two migraine severity grades (or two headache frequency groups) that represents a clinically significant difference in restrained eating levels. Using data from this pilot study two broad migraine severity groups were thus created for the purpose of comparing restrained eating scores. The PedMIDAS grades I and II were combined to create migraine severity group 1 (i.e. PedMIDAS scores 0 to 30). The PedMIDAS grades III and IV were then combined to create migraine severity group 2 (i.e. PedMIDAS scores greater than 31). The Mann-Whitney U test was used to compare the DEBQ (adolescent version) restrained eating scores (that were of non-parametric distribution) between these 2 migraine severity groups. As can be seen in table 4.8.1 there was no significant difference ($p \leq 0.05$) in restrained eating raw scores between the two migraine severity groups.

Test Statistic	DEBQ- Restrained eating raw mean scores
Mann-Whitney U	94.50
Wilcoxon W	28.45
Z-value	-0.43
p-value	0.67

Table 4.8.1- Mann-Whitney test results for comparison of DEBQ (for adolescsents) restrained eating raw scores

As this pilot study was the first study ever to investigate eating behaviours and migraines, no other data were available from which to extrapolate a minimum clinical difference in restrained eating scores with respect to migraines. Consequently a literature search was done to find a minimum clinical difference among non-migraine studies. However no study was identified that defined what minimum change in DEBQ restrained eating raw scores indicated the presence of clinically significant restrained eating behaviour. Although a minimum clinical difference has not yet been defined for restrained eating, previous studies have demonstrated various differences in DEBQ (adolescence version) restrained eating scores that represent clinically significant restrained eating behaviour (these can be seen in table 4.8.2). The studies from which the MCID values listed in table 4.8.2 were extrapolated are now discussed.

The MCID in mean DEBQ (adolescent version) restrained eating raw scores between obese and non-obese female college students (mean age = 23 years) in a study by Allison et al was 0.1[236]. In another study by Halvarsson et al[237] (sample= 117 girls aged 9 to 10 years) the clinically significant difference in DEBQ (adolescent version) restrained eating raw scores between groups of dieters and non-dieters was 0.7. It is purported that migraine will not have as strong an effect on restrained eating as dieting behaviour, so the MCID will be less than 0.7, but greater than 0.1. Following discussions with the statistician involved in the pilot study it has been decided to use a range of different MCID values to calculate different sample sizes. The values used for the minimum clinically important difference in restrained eating scores ranged from 0.1 to 0.7. The software “Stats Direct” was used to calculate the estimated sample based on a power of 0.8, alpha value (p-value) of 0.05 and a standard deviation of 0.96 (this was the s.d value for the DEBQ for adolescents restrained eating raw scores from this pilot study).

MCID (based on mean DEBQ for adolescents restrained eating raw scores)	No. of controls	No. of cases
0.1	1448	1448
0.2	363	363
0.3	162	162
0.4	92	92
0.5	59	59
0.6	42	42
0.7	31	31

Table 4.8.2- Sample size calculations based on different MCID values
Power= 0.8, Alpha (P-value) = 0.05, Standard Deviation= 0.96

Given that the recommended target sample size calculation will be based on an estimate of what is considered the MCID in restrained eating scores among migraine patients, there is no way to prove what the exact sample size should be for the main future study. Instead the aim is to ensure that the sample size chosen is based on a calculation from the most appropriate MCID value. The largest sample calculated which is practically achievable for recruitment is one of the criteria for choosing the most appropriate sample size for the main future study. Given that the MCID is purported to be below the level of 0.7 (as defined by Halvarsson et al[237]), but greater than the value of 0.1 (as defined by Allison et al[236]), a value of 0.3 would seem an appropriate estimate for the MCID value. As outlined in table 4.8.2, a sample size calculation based on a MCID value of 0.3 produces an estimated sample of 162 migraines cases and 162 controls. This is a large population size which would be feasible to recruit over a 2 year period (roughly 6 to 7 patients a month would have to be recruited). For these reasons it is recommended that for the main future study, a sample of 162 migraine cases and 162 controls be used as a target sample size.

The majority of headache patients referred to clinics at Alder Hey children's Hospital suffered from migraine. There was a lack of patients that fitted the control criteria for a non-migraine headache diagnosis and consequently enough control patients were not available for recruitment. For the future study it would be recommended to use a different target population from which to select control non-migraine patients. To avoid possible neurobiological overlap between migraines and non-migraine headaches[14], a suitable alternative would be to use headache free subjects as controls. This would mean expanding the study to include the recruitment of normal (headache-free) controls matched for age and sex from a school local to each migraine case.

There were many instances when numerous patients eligible for recruitment attended different clinics at the same time. Considering there was only one recruiting agent, it was not possible to recruit numerous patients all at once and in addition there was a lack of facilities (few rooms were available to accommodate the simultaneous recruitment of more than one patient). To help resolve this issue in the main future study, it would be recommended to have more than one recruiting agent and more rooms available for recruitment to take place. This would to allow the simultaneous recruitment of numerous patients.

There was a 28% refusal rate for patients approached to participate in this pilot study, which prolonged the time taken to recruit the target 60 migraine patients. The primary reason why 26 patients were unable to take part in the study was because parents were unable to spare 45 minutes for the recruitment phase. Some parents recommended that the researcher could make a home visit for patient recruitment. Although this is a possibility for the main future study, this method of home recruitment would be very time consuming and would require a more complicated revision of the study ethics approval.

Height and weight as used to calculate BMI was convenient but not necessarily the most accurate measure of adiposity in such a small population study[200]. With adequate funding more robust adiposity measurement techniques such as abdominal visceral fat MRI scanning could have been used, which is a relatively safe gold standard for determining

adiposity levels[195]. If this were to be incorporated into the future study design, more funding would be required and greater time investment needed per patient at recruitment.

The FIQ was not the most robust method of assessment of daily food intake because children were highly susceptible to recall bias when reporting on the FIQ. A prospective method of assessment of food intake such a food diary would avoid the problem of recall bias because patients would hopefully keep a record of foods eaten as they are eaten at each mealtime. Hence for the future study it is recommended that patients keep a prospective dietary record (food diary) of foods eaten each day[167]. As food diaries can be quite demanding of subjects, initial records are quite complete but this soon starts to deteriorate as time progresses[238]. To help avoid this it would be advisable to keep a food diary for only a short space of time (e.g. 5 days) which includes at least a weekend day (because food consumption on the weekend is usually different to that on a weekday[238]). Using this method of assessment for food intake would require following up each patient upon completion of the food diary and hence a longer duration of study period would be required. This method might provide more robust data with regards to exact types and amounts of foods eaten as well as the calculation of specific nutritional intake[167].

Based on the evidence to suggest a neurobiological overlap between migraines, appetite and adiposity, a study is needed to investigate the role of eating behaviours as a function of migraine pathology[118]. For this to be feasible a reliable and valid biomarker for migraine severity is required. Given that calcitonin gene related peptide levels increase during acute migraine attacks[119], CGRP could be used as a biomarker of migraine severity. Serum leptin levels as a biomarker for appetite could then be assessed for associations with CGRP levels alongside eating behaviours monitored in an ingestive laboratory[122]. As the hypothalamus is a common site of expression for neuropeptides involved in appetite and migraines, a future study could investigate the relationship between hypothalamic activity, serum CGRP/leptin levels, eating behaviours and migraine severity[124,125]. However these methods would involve using laboratory based methods for tracking biomarker levels and expensive neuro-imaging techniques (e.g. PET scans)[124] for identifying hypothalamic activity.

To find a significant relationship between migraines, eating behaviours and adiposity a prospective follow up of patients over a long term period of time may be required. No study has ever investigated the long term follow up of migraine patients to assess adiposity levels. The "Avon Longitudinal Study of Parents and Children" (ASPAC) initially set up in 1991 at Bristol University have followed up children from 14,000 pregnant women since birth. It contains data from two family generations. It has gathered information on all-of-life data including repeated measures of height, weight, dietary intake, social circumstances, medical conditions including recurrent headaches disorders such as migraines, and biophysical measures of physical activity and adiposity. Researchers of the ALSPAC study have already been contacted about sharing data on migraines, adiposity and diet to compare with data in the main future study. As the ASLPAC study has recorded data since birth, the temporal relationship between migraine development and obesity onset can be analysed whilst identifying confounding factors[239].

This cross-sectional pilot study found that the CEBQ desire to drink subscale had a weak but significantly positive correlation with the PedMIDAS scores and the FIQ negative marker subscale scores had a weak but significantly positive correlation with monthly headache frequency. Both the internalising subscale of the CBCL and the total CBCL scale had a weak but significantly positive correlation with the PedMIDAS scores and BMI z-scores. Eating behaviours, food cravings and adiposity shared no significant relationship with either of the migraine measures used in this pilot study (migraine severity/monthly headache frequency). Although no firm conclusions can be drawn due to limitations in the methodology, this pilot study provides a foundation for future research on migraines, eating behaviours, thirst levels and food intake.

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It must be noted that references with a journal name containing more than one word was abbreviated.

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Chapter 5.1.0- Appendix

Chapter 5.1.1a

Search strategy used to identify headache-obesity studies reviewed in chapter 1.1 (Migraines- Migraine and adiposity).

Articles were searched using the various electronic data bases listed in table 5.1. MeSH terms (see table 5.2) were used to begin broad searches for any current literature available on headaches and obesity. The results from various MeSH terms were later combined to provide a more narrow and focussed search strategy. For example the following MeSH terms were combined; “migraine”, “headaches” and “obesity” to gain search results for studies which contained all three key items (see tables 5.3 and 5.4).

Resources	Description
Data base searches	Medline was searched using: Ovid, Pub med and the BMA's search engine.
Secondary sources	Cochrane library, Google Scholar, Books from University of Liverpool library and Internet resources.
Cross referencing	Reference lists from review articles were used to find the desired journals.
Electronic online journals	These were searched by accessing the specific journal contents, using the library catalogue at Liverpool University.

Table 5.1- Resources used to search for headache-obesity studies

MeSH terms	Limits applied
Headache	Full text + 1990-2010
Migraine	Full text + 1990-2010
Obesity	Full text + 1990-2010
Adiposity	Full text + 1990-2010
Children/ Paediatric	Full text + 1990-2010
Chronic daily headache	Full text + 1990-2010
Appetite	Full text + 1990-2010

Table 5.2- MeSH terms used to search for headache-obesity articles

#	Search History	Results	Display
1	Migraine.mp. [mp=title, abstract, full text, caption text]	7692	DISPLAY
2	limit 1 to yr="2000 - 2010"	492	DISPLAY
3	Headache.mp. [mp=title, abstract, full text, caption text]	13020	DISPLAY
4	limit 3 to yr="2000 - 2010"	9731	DISPLAY
5	Obesity.mp. [mp=title, abstract, full text, caption text]	8820	DISPLAY
6	limit 5 to yr="2000 - 2010"	5964	DISPLAY
7	Adiposity]	749	DISPLAY
8	limit 7 to yr="2000 - 2010"	52	DISPLAY

Table 5.3- Number of hits displayed for each MeSH term used

#	Search History	Results	Display
9	2 or 4	13674	DISPLAY
10	6 or 8	82	DISPLAY
11	9 and 10	46	DISPLAY

Table 5.4- Number of hits displayed for each MeSH term used

Chapter 5.1.1b
The STROBE criteria

Criteria	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
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
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
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
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, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
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
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
Outcome data	15*	Report numbers of outcome events or summary measures
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
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
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
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
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

Table 5.5- Criteria used to review the headache-obesity studies in chapter 1.1.1 as adapted from the STROBE criteria

Chapter 5.1.2
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 migraine.

Why have you and your child been chosen?
Based on the records at Alder Hey 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, Alder Hey 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.

Chapter 5.1.3
Migraine pro-forma

Alder Hey Children's NHS
NHS Foundation Trust

Migraine Proforma for migraine, appetite behaviour and obesity study:

Patient Identification number:.....

Sex: M / F Age:..... Age of onset:.....

Duration of headache:..... Number of attacks: ..... Intensity:

< 4..... Mild.....

4-10..... Moderate.....

>10 ..... Severe.....

Symptoms:

Nausea..... Lacrimation..... Miosis.....

Vomiting..... Conjuctival injection..... Ptosis.....

Phonophobia..... Nasal congestion..... Eyelid oedema.....

Photophobia..... Forehead and facial sweating..... Vertigo.....

Anorexia..... Nasal congestion.....

Exacerbating factors :.....Relieving factors:.....

Aura symptoms:

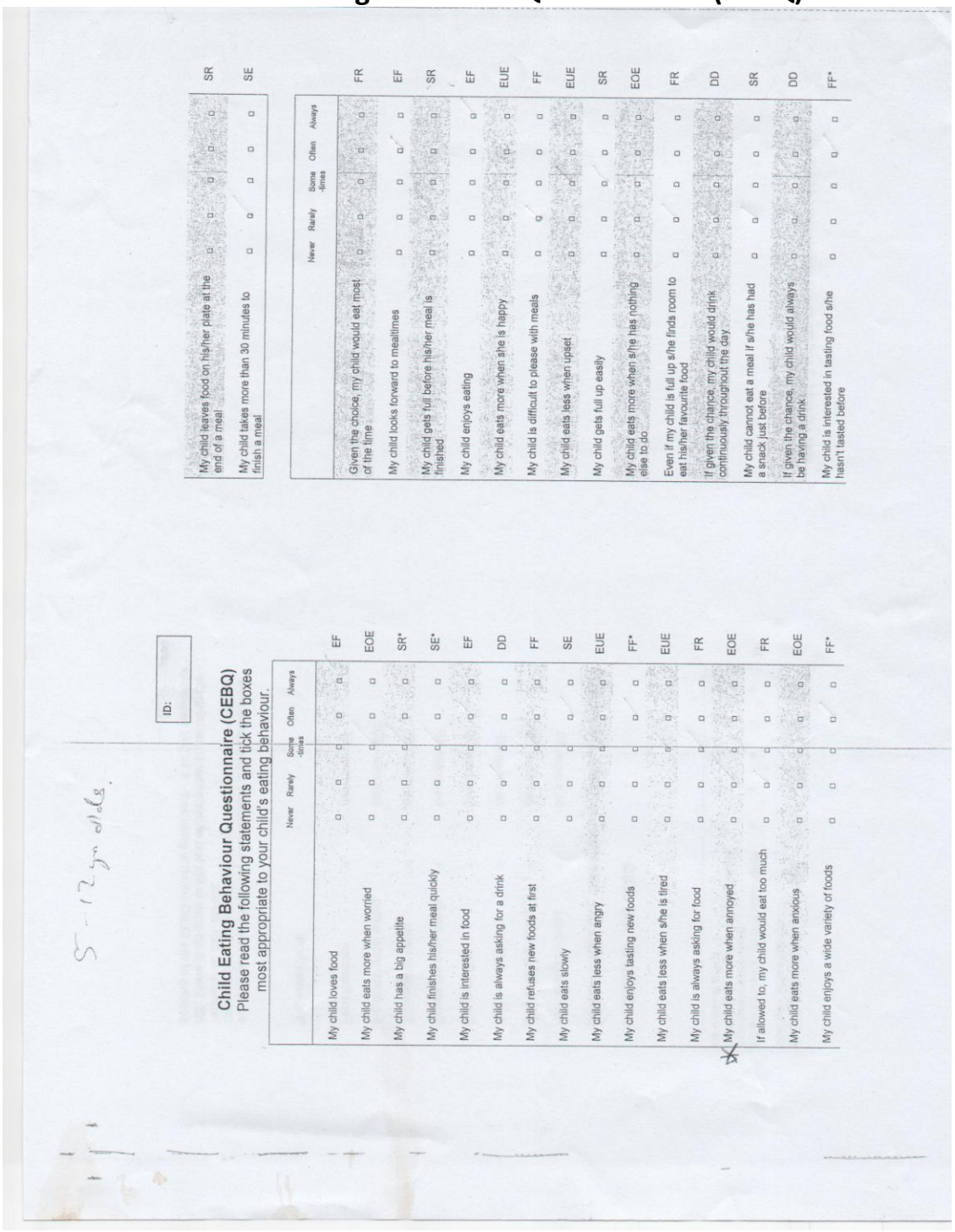
Visual..... Sensorial..... Motor.....

Speech aura..... Less typical aura.....

Fhx: Y / N
Relative(s).....

Benign paroxysmal vertigo Y / N

Chapter 5.1.4
Children's Eating Behaviour Questionnaire (CEBQ)



Child Eating Behaviour Questionnaire (CEBQ)

Please read the following statements and tick the boxes most appropriate to your child's eating behaviour.

ID:

	Never	Rarely	Some-times	Often	Always	
My child loves food	☐	☐	☐	☐	☐	EF
My child eats more when worried	☐	☐	☐	☐	☐	EOE
My child has a big appetite	☐	☐	☐	☐	☐	SR*
My child finishes his/her meal quickly	☐	☐	☐	☐	☐	SE*
My child is interested in food	☐	☐	☐	☐	☐	EF
My child is always asking for a drink	☐	☐	☐	☐	☐	DD
My child refuses new foods at first	☐	☐	☐	☐	☐	FF
My child eats slowly	☐	☐	☐	☐	☐	SE
My child eats less when angry	☐	☐	☐	☐	☐	EUE
My child enjoys tasting new foods	☐	☐	☐	☐	☐	FF*
My child eats less when s/he is tired	☐	☐	☐	☐	☐	EUE
My child is always asking for food	☐	☐	☐	☐	☐	FR
My child eats more when annoyed	☐	☐	☐	☐	☐	EOE
If allowed to, my child would eat too much	☐	☐	☐	☐	☐	FR
My child eats more when anxious	☐	☐	☐	☐	☐	EOE
My child enjoys a wide variety of foods	☐	☐	☐	☐	☐	FF*
My child leaves food on his/her plate at the end of a meal	☐	☐	☐	☐	☐	SR
My child takes more than 30 minutes to finish a meal	☐	☐	☐	☐	☐	SE
Given the choice, my child would eat most of the time	☐	☐	☐	☐	☐	FR
My child looks forward to mealtimes	☐	☐	☐	☐	☐	EF
My child gets full before his/her meal is finished	☐	☐	☐	☐	☐	SR
My child enjoys eating	☐	☐	☐	☐	☐	EF
My child eats more when she is happy	☐	☐	☐	☐	☐	EUE
My child is difficult to please with meals	☐	☐	☐	☐	☐	FF
My child eats less when upset	☐	☐	☐	☐	☐	EUE
My child gets full up easily	☐	☐	☐	☐	☐	SR
My child eats more when s/he has nothing else to do	☐	☐	☐	☐	☐	EOE
Even if my child is full up s/he finds room to eat his/her favourite food	☐	☐	☐	☐	☐	FR
If given the chance, my child would drink continuously throughout the day	☐	☐	☐	☐	☐	DD
My child cannot eat a meal if s/he has had a snack just before	☐	☐	☐	☐	☐	SR
If given the chance, my child would always be having a drink	☐	☐	☐	☐	☐	DD
My child is interested in tasting food s/he hasn't tasted before	☐	☐	☐	☐	☐	FF*

My child decides that s/he doesn't like a food, even without tasting it	□	□	□	□	□	FF
If given the chance, my child would always have food in his/her mouth	□	□	□	□	□	FR
My child eats more and more slowly during the course of a meal	□	□	□	□	□	SE

were scored 1- 5 and the means and standard deviations given in the tables reflect this.

SCORING OF THE CEBQ

(Never=1, Rarely=2, Sometimes=3, Often=4, Always=5)

Food responsiveness = item mean FR

Emotional over-eating = item mean EOE

Enjoyment of food = item mean EF

Desire to drink = item mean DD

Satiety responsiveness = item mean SR

Slowness in eating = item mean SE

Emotional under-eating = item mean EUE

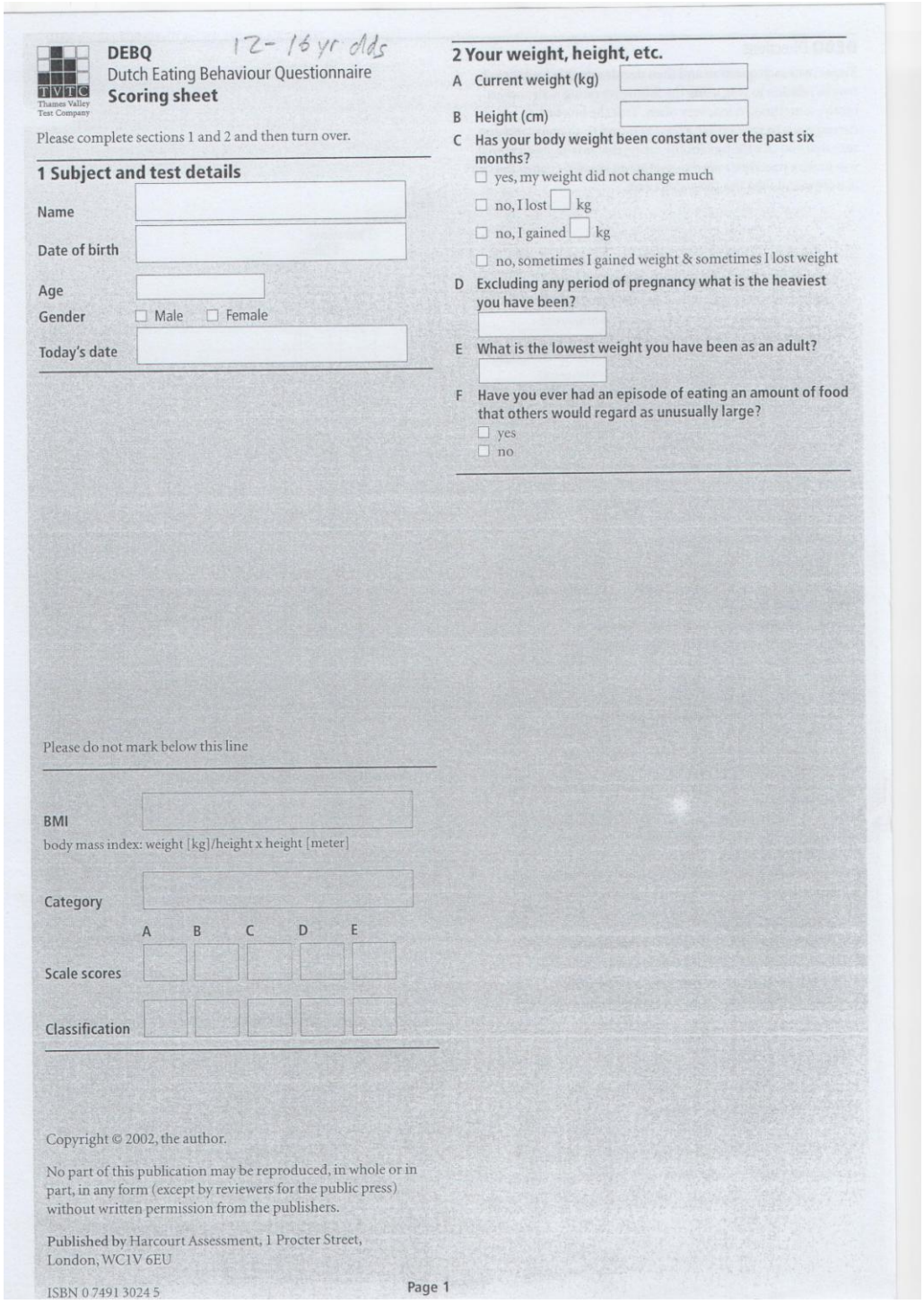
Food fussiness = item mean FF

*Reversed items

Wardle, J, Guthrie CA, Sanderson, S and Rapoport, L. Development of the Children's Eating Behaviour Questionnaire. *Journal of Child Psychology and Psychiatry*. 42, 2001, 963-970.

NB: There is an error in the text of this paper concerning the scoring of the CEBQ which is given as 0 - 4. In fact responses

Chapter 5.1.5a
Dutch Eating Behaviour Questionnaire (DEBQ) for adolescents (12- 16 years)



TVTC
Thames Valley Test Company

DEBQ 12- 16 yr olds
Dutch Eating Behaviour Questionnaire
Scoring sheet

Please complete sections 1 and 2 and then turn over.

1 Subject and test details

Name
Date of birth
Age
Gender ☐ Male ☐ Female
Today's date

2 Your weight, height, etc.

A Current weight (kg)
B Height (cm)
C Has your body weight been constant over the past six months?
☐ yes, my weight did not change much
☐ no, I lost ☐ kg
☐ no, I gained ☐ kg
☐ no, sometimes I gained weight & sometimes I lost weight
D Excluding any period of pregnancy what is the heaviest you have been?
E What is the lowest weight you have been as an adult?
F Have you ever had an episode of eating an amount of food that others would regard as unusually large?
☐ yes
☐ no

Please do not mark below this line

BMI
body mass index: weight [kg]/height x height [meter]

Category

	A	B	C	D	E
Scale scores					
Classification					

Published by Harcourt Assessment, 1 Procter Street, London, WC1V 6EU

ISBN 0 7491 3024 5

Page 1

DEBQ Directions

Please read each question and then decide whether each item is true in relation to you, using the following rating scale: never; rarely; sometimes; often; very often. Tick the box that corresponds to your rating. Please respond to all items, making sure that you tick the box for the rating that is true about you. If you make a mistake or need to change an answer, change the tick to a cross and then tick the correct box.

		1 Never	2 Rarely	3 Sometimes	4 Often	5 Very often
1	Do you have the desire to eat when you are irritated?	☐	☐	☐	☐	☐
2	If food tastes good to you, do you eat more than usual?	☐	☐	☐	☐	☐
3	Do you have a desire to eat when you have nothing to do?	☐	☐	☐	☐	☐
4	If you have put on weight, do you eat less than you usually do?	☐	☐	☐	☐	☐
5	Do you have a desire to eat when you are depressed or discouraged?	☐	☐	☐	☐	☐
6	If food smells and looks good, do you eat more than usual?	☐	☐	☐	☐	☐
7	How often do you refuse food or drink offered because you are concerned about your weight?	☐	☐	☐	☐	☐
8	Do you have a desire to eat when you are feeling lonely?	☐	☐	☐	☐	☐
9	If you see or smell something delicious, do you have a desire to eat it?	☐	☐	☐	☐	☐
10	Do you have a desire to eat when somebody lets you down?	☐	☐	☐	☐	☐
11	Do you try to eat less at mealtimes than you would like to eat?	☐	☐	☐	☐	☐
12	If you have something delicious to eat, do you eat it straight away?	☐	☐	☐	☐	☐
13	Do you have a desire to eat when you are cross?	☐	☐	☐	☐	☐
14	Do you watch exactly what you eat?	☐	☐	☐	☐	☐
15	If you walk past the baker do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
16	Do you have a desire to eat when you are approaching something unpleasant to happen?	☐	☐	☐	☐	☐
17	Do you deliberately eat foods that are slimming?	☐	☐	☐	☐	☐
18	If you see others eating, do you also have the desire to eat?	☐	☐	☐	☐	☐
19	When you have eaten too much, do you eat less than usual the following days?	☐	☐	☐	☐	☐
20	Do you get the desire to eat when you are anxious, worried or tense?	☐	☐	☐	☐	☐
21	Do you find it hard to resist eating delicious foods?	☐	☐	☐	☐	☐
22	Do you deliberately eat less in order not to become heavier?	☐	☐	☐	☐	☐
23	Do you have a desire to eat when things are going against you or when things have gone wrong?	☐	☐	☐	☐	☐
24	If you walk past a snack bar or a café, do you have the desire to buy something delicious?	☐	☐	☐	☐	☐
25	Do you have the desire to eat when you are emotionally upset?	☐	☐	☐	☐	☐
26	How often do you try not to eat between meals because you are watching your weight?	☐	☐	☐	☐	☐
27	Do you eat more than usual, when you see others eating?	☐	☐	☐	☐	☐
28	Do you have a desire to eat when you are bored or restless?	☐	☐	☐	☐	☐
29	How often in the evening do you try not to eat because you are watching your weight?	☐	☐	☐	☐	☐
30	Do you have a desire to eat when you are frightened?	☐	☐	☐	☐	☐
31	Do you take into account your weight with what you eat?	☐	☐	☐	☐	☐
32	Do you have a desire to eat when you are disappointed?	☐	☐	☐	☐	☐
33	When you are preparing a meal are you inclined to eat something?	☐	☐	☐	☐	☐
		1 Never	2 Rarely	3 Sometimes	4 Often	5 Very often

Please do not mark below this line

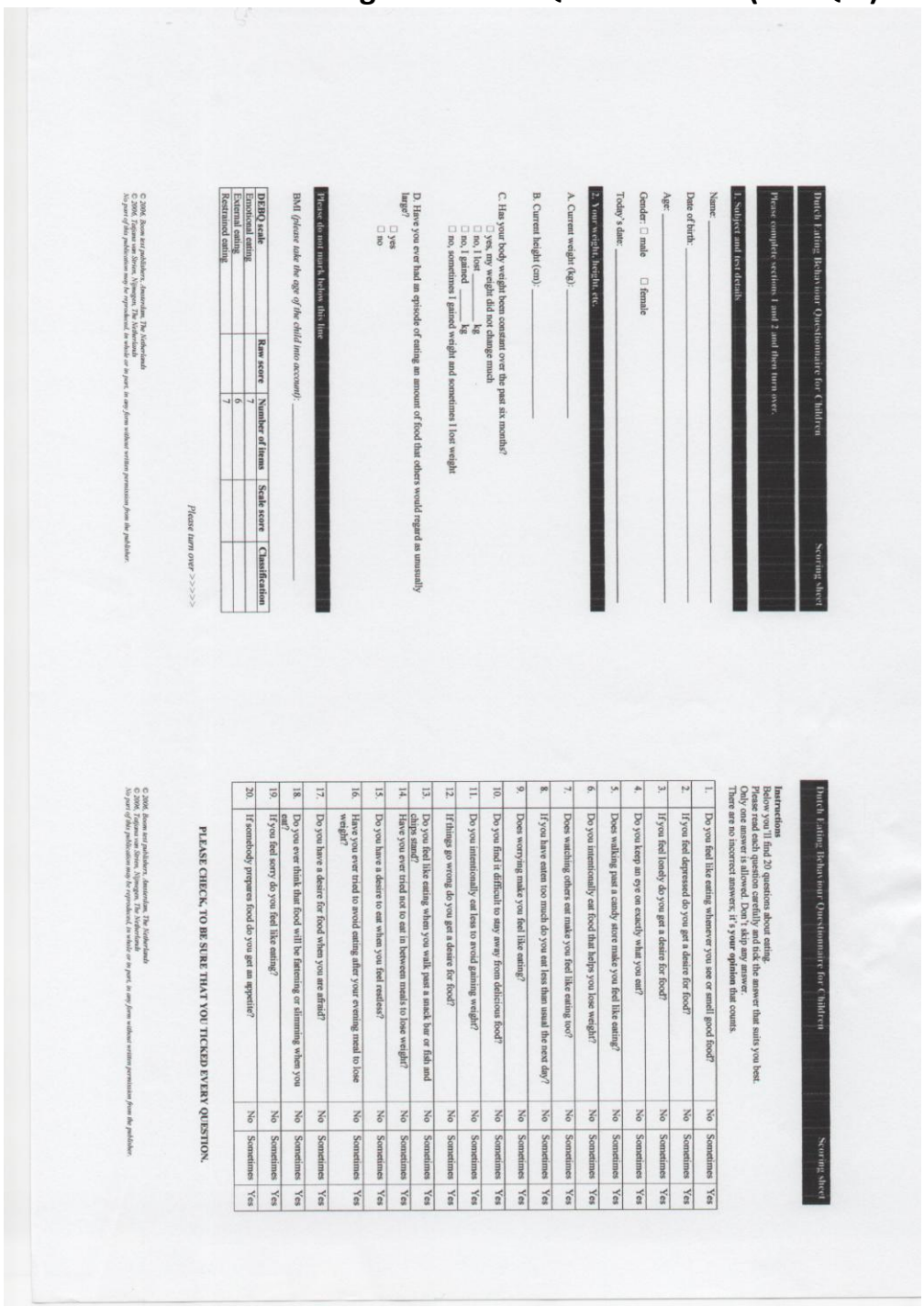
Raw score ☐☐☐☐☐

/ Number of items ☐☐☐☐☐

= Scale score ☐☐☐☐☐

Page 2

Chapter 5.1.5b
Children's Dutch Eating Behaviour Questionnaire (DEBQ-C)



Dutch Eating Behaviour Questionnaire for Children — Scoring Sheet

Please complete sections 1 and 2 and then turn over.

1. Subject and test details

Name: _____

Date of birth: _____

Age: _____

Gender: ☐ male ☐ female

Today's date: _____

2. Your weight, height etc.

A. Current weight (kg): _____

B. Current height (cm): _____

C. Has your body weight been constant over the past six months?
- ☐ yes, my weight did not change much
- ☐ no, I lost _____ kg
- ☐ no, I gained _____ kg
- ☐ no, sometimes I gained weight and sometimes I lost weight

D. Have you ever had an episode of eating an amount of food that others would regard as unusually large?
- ☐ yes
- ☐ no

Please do not mark below this line

BMI *(please take the age of the child into account)*: _____

DEBQ scale	Raw score	Number of items	Scale score	Classification
Emotional eating	7			
External eating	6			
Restrained eting	7			

Please turn over >>>>>

Dutch Eating Behaviour Questionnaire for Children — Scoring Sheet

Instructions
Below you'll find 20 questions about eating.
Please read each question carefully and tick the answer that suits you best.
Only one answer is allowed. Don't skip any answer.
There are no incorrect answers; it's **your opinion** that counts.

1.	Do you feel like eating whenever you see or smell good food?	No	Sometimes	Yes
2.	If you feel depressed do you get a desire for food?	No	Sometimes	Yes
3.	If you feel lonely do you get a desire for food?	No	Sometimes	Yes
4.	Do you keep an eye on exactly what you eat?	No	Sometimes	Yes
5.	Does walking past a candy store make you feel like eating?	No	Sometimes	Yes
6.	Do you intentionally eat food that helps you lose weight?	No	Sometimes	Yes
7.	Does watching others eat make you feel like eating too?	No	Sometimes	Yes
8.	If you have eaten too much do you eat less than usual the next day?	No	Sometimes	Yes
9.	Does worrying make you feel like eating?	No	Sometimes	Yes
10.	Do you find it difficult to stay away from delicious food?	No	Sometimes	Yes
11.	Do you intentionally eat less to avoid gaining weight?	No	Sometimes	Yes
12.	If things go wrong do you get a desire for food?	No	Sometimes	Yes
13.	Do you feel like eating when you walk past a snack bar or fish and chips stand?	No	Sometimes	Yes
14.	Have you ever tried not to eat in between meals to lose weight?	No	Sometimes	Yes
15.	Do you have a desire to eat when you feel restless?	No	Sometimes	Yes
16.	Have you ever tried to avoid eating after your evening meal to lose weight?	No	Sometimes	Yes
17.	Do you have a desire for food when you are afraid?	No	Sometimes	Yes
18.	Do you ever think that food will be fattening or slimming when you eat?	No	Sometimes	Yes
19.	If you feel sorry do you feel like eating?	No	Sometimes	Yes
20.	If somebody prepares food do you get an appetite?	No	Sometimes	Yes

PLEASE CHECK, TO BE SURE THAT YOU TICKED EVERY QUESTION.

Chapter 5.1.6
Food Intake Questionnaire (FIQ)

Liverpool John Moores University
Faculty of Education, Community and Leisure
Centre for Consumer Education & Research

What did *YOU* eat and drink yesterday?
These questions are very important. Please answer them very carefully.
All your answers will be kept secret. Please leave blank:

ID: [ ] [ ] [ ] [ ] [ ] [ ]
Date: _____, 200_ [ ] [ ] [ ] [ ] [ ] [ ]

About yourself:
What is your name? (eg Alex Smith) _____

How old are you (numbers only)? _____

Are you a boy or a girl (B or G)? _____

What is your postcode (e.g. L23 6JT)? _____

What school do you go to? _____

Do you get a free school meal? (Please tick the box) **Yes** [ ] **No** [ ]

Please tick a box to answer Yes or No or leave box empty.

Yesterday, did you have anything at all:		Yes	No	
to eat or drink before leaving home to come to school?	[ ]	[ ]		
to eat or drink on your way to school?		[ ]	[ ]	
Yesterday, did you:				
Eat or drink nothing at lunch time?			[ ]	[ ]
Eat a school lunch?		[ ]	[ ]	
Eat a packed lunch from home?		[ ]	[ ]	
Go home for your lunch?			[ ]	[ ]
Eat out of school but not at home?			[ ]	[ ]

Did you at any time yesterday eat any amount of any of the following:

Breakfast cereals:				
Frosties or Sugar Puffs, Ricicles, Coco Pops? Negative Sugary	[ ]	[ ]		
Branflakes or Weetabix, Allbran, Branbuds, Sultana Bran, Fruit 'n' fibre? Positive Fibrous	[ ]	[ ]		
Muesli or Shredded Wheat, Porridge, Ready Brek? Positive Fibrous		[ ]	[ ]	
Rice Krispies or Cornflakes, Puffed Wheat, Pufa Pufa Rice? *****		[ ]	[ ]	
Bread:				
White bread (slices or buns)? *****		[ ]	[ ]	
Brown or wholemeal bread any type (slices or buns)? Positive Fibrous		[ ]	[ ]	

Butter or margarine (including on bread, crispbread, potatoes or vegetables etc)?
If you had any butter or margarine yesterday do you think that it was:

Butter:		Negative Fatty	[ ]	[ ]
Hard margarine: eg Stork, Echo?	Negative Fatty		[ ]	[ ]
Ordinary soft margarine: eg Blue Band, Summer County?	Negative Fatty		[ ]	[ ]
Polyunsaturated spread: eg Vitalite or Flora?		Positive	[ ]	[ ]
Low fat spread: eg Outline, Gold, Freeway, Hi-life or Delight?	Positive		[ ]	[ ]

Did you at any time yesterday eat any amount of any of the following:	Yes	No
Biscuits:		
Plain biscuits eg malted milk, Digestives, Rich Tea etc? **Negative Sugary**	[ ]	[ ]
Any biscuits which were covered all over in chocolate: eg Kit-Kat, Penguin, United etc? Negative Sugary [ ] [ ]		
Cakes and puddings:		
Any sort of cake, Swiss roll (plain or chocolate), doughnuts scones, individual pies, jam tarts, custard tarts etc? **Negative Sugary**	[ ]	[ ]
Any sort of pudding: Fruit pie, sponge pudding, tinned fruit, jelly, trifle, lemon meringue, cheesecake, milk pudding (like rice, semolina, tapioca, custard etc) etc? **Negative Sugary**	[ ]	
Sweets & chocolates:		
Sweets such as: boiled sweets, fruit gums or pastilles, liquorice, jelly sweets, chews, toffees, chewing gum etc? **Negative Sugary**	[ ]	[ ]
Chocolates or chocolate bars like: Quality Street, Rolos, Mars Bar, Twix? **Negative Sugary**	[ ]	[ ]
Ice cream, choc-ices, ice lollies, ice-pops? **Negative Sugary**	[ ]	[ ]
Sugar:		
Sugar (white or brown) in any drink such as tea, coffee, cocoa etc **Negative Sugary**	[ ]	[ ]
Sugar (white or brown) on any food such as cornflakes or pancakes? **Negative Sugary**	[ ]	[ ]
An artificial sweetener (like saccharin, sweetex, sweet'n'low, canderel etc)? **Positive**	[ ]	[ ]
Potatoes:		
Boiled potatoes? *****	[ ]	[ ]
Mashed potatoes? *****	[ ]	[ ]
Baked or jacket potatoes? **Positive** High fibre	[ ]	[ ]
Roast potatoes? **Negative Fatty**	[ ]	[ ]
Chips? **Negative Fatty**	[ ]	[ ]
Crisps (any type or flavour)? **Negative Fatty**	[ ]	[ ]
Fruit:		
Any fresh fruit such as apples, oranges (any type), pears, bananas, plums etc? **Positive**	[ ]	[ ]
Vegetables:		
Baked beans? *****	[ ]	[ ]
Any type of salad such as: celery, tomatoes, lettuce, cucumber, celery etc? **Positive**	[ ]	[ ]
Any fried vegetables eg Fried onions, fried mushrooms or fried tomatoes etc? **Negative Fatty**	[ ]	[ ]
Any other vegetables eg Peas, cabbage, carrots, leeks, green beans, kidney beans, **Positive** parsnips, tinned tomatoes, cauliflower, leeks, turnips or sprouts etc?	[ ]	[ ]
Meat		
Ordinary burger? **Negative Fatty**	[ ]	[ ]
Ordinary sausages? **Negative Fatty**	[ ]	[ ]
Low fat burger? **Positive**	[ ]	[ ]
Low fat sausages? **Positive**	[ ]	[ ]
Meat pie, Cornish pastie or sausage roll etc? **Negative Fatty**	[ ]	[ ]
Any other type of meat eg Minced meat, steak, ham, chicken etc?	[ ]	[ ]
Fish		
Fish fried in batter? **Negative Fatty**	[ ]	[ ]
Any other types fish eg fish fingers or tinned - sardines, tuna, pilchards, etc? **Positive**	[ ]	[ ]

Did you at any time yesterday eat any amount of any of the following:	Yes	No

---

Eggs
Boiled or Poached?? [ ] [ ]
Scrambled or Fried? **Negative Fatty** [ ] [ ]

Cheese
Cheese eg Cheddar, Leicester, Cheshire? **Negative Fatty** [ ] [ ]
Soft cheese eg Philadelphia, Dairy Lea? **Negative Fatty** [ ] [ ]
Low fat cheese eg Shape or Philidelphia lite? Positive [ ] [ ]

Take-away food
Chip shop food or Chinese, Indian, Curries, Pizza, Kebabs etc? **Negative Fatty** [ ] [ ]

Did you put any Salt on your food? **Negative** [ ] [ ]

Fizzy drinks (like: lemonade, soda stream, Coca-Cola, Pepsi, 7-UP, Fanta etc):
If you had any fizzy drink yesterday do you think that it was:
Diet or low calorie sort of fizzy drink? **Positive** [ ] [ ]
Regular or ordinary fizzy drink? **Negative Sugary** [ ] [ ]

Still cordials (which you add water to like: orange squash, Ribena, Barley water etc)?
If you had any still cordial yesterday do you think that it was:
Diet or low calorie sort of still drink? **Positive** [ ] [ ] Regular or ordinary still drink? **Negative Sugary** [ ] [ ]

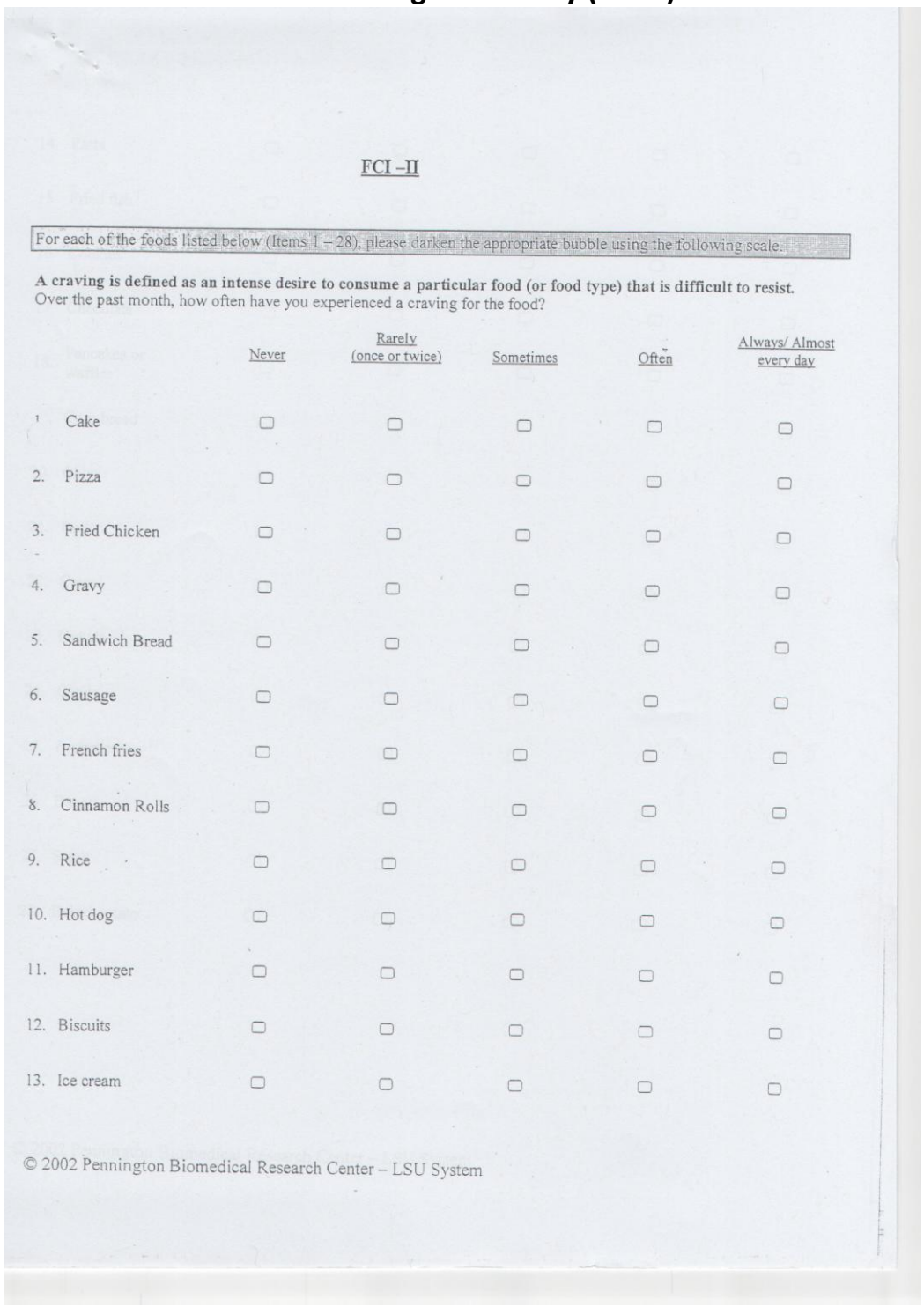
Milk (including milk in tea, coffee, milkshakes, flavoured milk, cocoa or on cereals etc)?
If you had any milk yesterday do you think that it was:
Ordinary full fat milk? **Negative Fatty** [ ] [ ]
Semi-skimmed or skimmed milk? **Positive** [ ] [ ]

Water **Positive** [ ] [ ]

Alcoholic drinks:
Beer, lager or cider [ ] [ ]
Wine [ ] [ ]
Sherry, Port, Martini, Cinzano, Pony, Cherry-B [ ] [ ]
Spirits such as whiskey, gin, brandy, vodka, rum Bacadi or Pernod [ ] [ ]

Many Thanks For Your Help!

Chapter 5.1.7
Food Cravings Inventory (FCI-II)



FCI –II

For each of the foods listed below (Items 1 – 28), please darken the appropriate bubble using the following scale.

A craving is defined as an intense desire to consume a particular food (or food type) that is difficult to resist.
Over the past month, how often have you experienced a craving for the food?

	Never	Rarely (once or twice)	Sometimes	Often	Always/ Almost every day
1. Cake	▢	▢	▢	▢	▢
2. Pizza	▢	▢	▢	▢	▢
3. Fried Chicken	▢	▢	▢	▢	▢
4. Gravy	▢	▢	▢	▢	▢
5. Sandwich Bread	▢	▢	▢	▢	▢
6. Sausage	▢	▢	▢	▢	▢
7. French fries	▢	▢	▢	▢	▢
8. Cinnamon Rolls	▢	▢	▢	▢	▢
9. Rice	▢	▢	▢	▢	▢
10. Hot dog	▢	▢	▢	▢	▢
11. Hamburger	▢	▢	▢	▢	▢
12. Biscuits	▢	▢	▢	▢	▢
13. Ice cream	▢	▢	▢	▢	▢

Author: Shashi Singh

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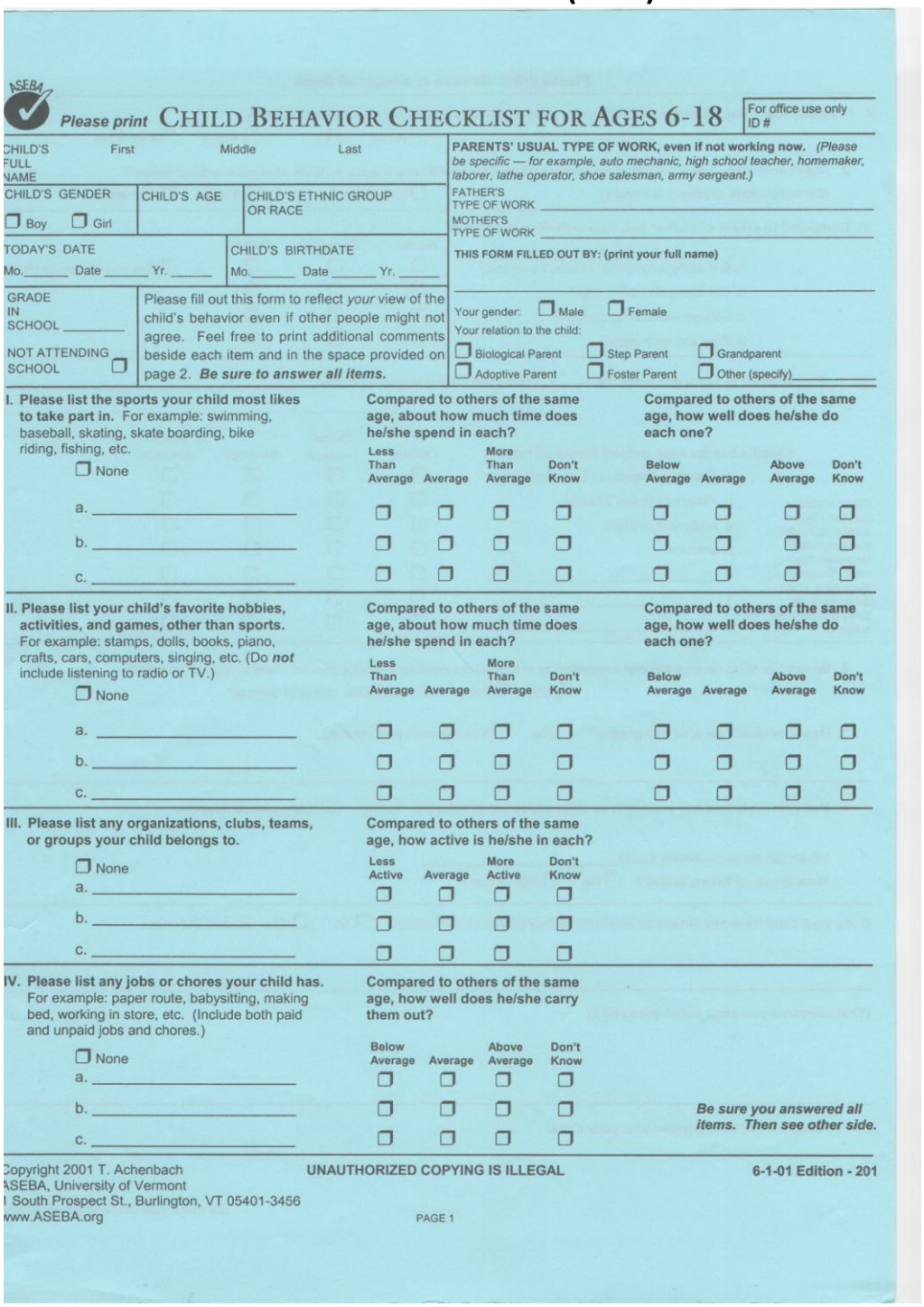
14. Pasta	☐	☐	☐	☐	☐
15. Fried fish	☐	☐	☐	☐	☐
16. Cookies	☐	☐	☐	☐	☐
17. Chocolate	☐	☐	☐	☐	☐
18. Pancakes or waffles	☐	☐	☐	☐	☐
. Corn bread	☐	☐	☐	☐	☐
20. Chips	☐	☐	☐	☐	☐
21. Rolls	☐	☐	☐	☐	☐
22. Cereal	☐	☐	☐	☐	☐
23. Donuts	☐	☐	☐	☐	☐
24. Candy	☐	☐	☐	☐	☐
25. Brownies	☐	☐	☐	☐	☐
26. Bacon	☐	☐	☐	☐	☐
27. Steak	☐	☐	☐	☐	☐
28. Baked potato	☐	☐	☐	☐	☐

Chapter 5.1.8
Child Behaviour Checklist (CBCL) tool



ASEBA

Please print **CHILD BEHAVIOR CHECKLIST FOR AGES 6-18**

For office use only ID #

CHILD'S FULL NAME: First Middle Last

CHILD'S GENDER ☐ Boy ☐ Girl | CHILD'S AGE | CHILD'S ETHNIC GROUP OR RACE

TODAY'S DATE Mo._____ Date _____ Yr. _____ | CHILD'S BIRTHDATE Mo._____ Date _____ Yr. _____

GRADE IN SCHOOL _____ ☐ NOT ATTENDING SCHOOL

Please fill out this form to reflect *your* view of the child's behavior even if other people might not agree. Feel free to print additional comments beside each item and in the space provided on page 2. ***Be sure to answer all items.***

PARENTS' USUAL TYPE OF WORK, even if not working now. *(Please be specific — for example, auto mechanic, high school teacher, homemaker, laborer, lathe operator, shoe salesman, army sergeant.)*

FATHER'S TYPE OF WORK _____

MOTHER'S TYPE OF WORK _____

THIS FORM FILLED OUT BY: (print your full name)

_____

Your gender: ☐ Male ☐ Female

Your relation to the child:

☐ Biological Parent ☐ Step Parent ☐ Grandparent

☐ Adoptive Parent ☐ Foster Parent ☐ Other (specify)_____

I. Please list the sports your child most likes to take part in. For example: swimming, baseball, skating, skate boarding, bike riding, fishing, etc.

☐ None

	Compared to others of the same age, about how much time does he/she spend in each?				Compared to others of the same age, how well does he/she do each one?			
	Less Than Average	Average	More Than Average	Don't Know	Below Average	Average	Above Average	Don't Know
a. _____	☐	☐	☐	☐	☐	☐	☐	☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐

II. Please list your child's favorite hobbies, activities, and games, other than sports. For example: stamps, dolls, books, piano, crafts, cars, computers, singing, etc. (Do ***not*** include listening to radio or TV.)

☐ None

	Compared to others of the same age, about how much time does he/she spend in each?				Compared to others of the same age, how well does he/she do each one?			
	Less Than Average	Average	More Than Average	Don't Know	Below Average	Average	Above Average	Don't Know
a. _____	☐	☐	☐	☐	☐	☐	☐	☐
b. _____	☐	☐	☐	☐	☐	☐	☐	☐
c. _____	☐	☐	☐	☐	☐	☐	☐	☐

III. Please list any organizations, clubs, teams, or groups your child belongs to.

☐ None

	Compared to others of the same age, how active is he/she in each?			
	Less Active	Average	More Active	Don't Know
a. _____	☐	☐	☐	☐
b. _____	☐	☐	☐	☐
c. _____	☐	☐	☐	☐

IV. Please list any jobs or chores your child has. For example: paper route, babysitting, making bed, working in store, etc. (Include both paid and unpaid jobs and chores.)

☐ None

	Compared to others of the same age, how well does he/she carry them out?			
	Below Average	Average	Above Average	Don't Know
a. _____	☐	☐	☐	☐
b. _____	☐	☐	☐	☐
c. _____	☐	☐	☐	☐

Be sure you answered all items. Then see other side.

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Please print. Be sure to answer all items.

V. 1. About how many close friends does your child have? (Do *not* include brothers & sisters)

❒ None ❒ 1 ❒ 2 or 3 ❒ 4 or more

2. About how many times a week does your child do things with any friends outside of regular school hours? (Do *not* include brothers & sisters)

❒ Less than 1 ❒ 1 or 2 ❒ 3 or more

VI. Compared to others of his/her age, how well does your child:

	Worse	Average	Better	
a. Get along with his/her brothers & sisters?	❒	❒	❒	❒ Has no brothers or sisters
b. Get along with other kids?	❒	❒	❒	
c. Behave with his/her parents?	❒	❒	❒	
d. Play and work alone?	❒	❒	❒	

VII. 1. Performance in academic subjects. ❒ Does not attend school because _____

Check a box for each subject that child takes	Failing	Below Average	Average	Above Average
a. Reading, English, or Language Arts	❒	❒	❒	❒
b. History or Social Studies	❒	❒	❒	❒
c. Arithmetic or Math	❒	❒	❒	❒
d. Science	❒	❒	❒	❒
e. _____	❒	❒	❒	❒
f. _____	❒	❒	❒	❒
g. _____	❒	❒	❒	❒

Other academic subjects–for example: computer courses, foreign language, business. Do *not* include gym, shop, driver's ed., or other nonacademic subjects.

2. Does your child receive special education or remedial services or attend a special class or special school?

❒ No ❒ Yes—kind of services, class, or school:

3. Has your child repeated any grades? ❒ No ❒ Yes—grades and reasons:

4. Has your child had any academic or other problems in school? ❒ No ❒ Yes—please describe:

When did these problems start?_____

Have these problems ended? ❒ No ❒ Yes–when?

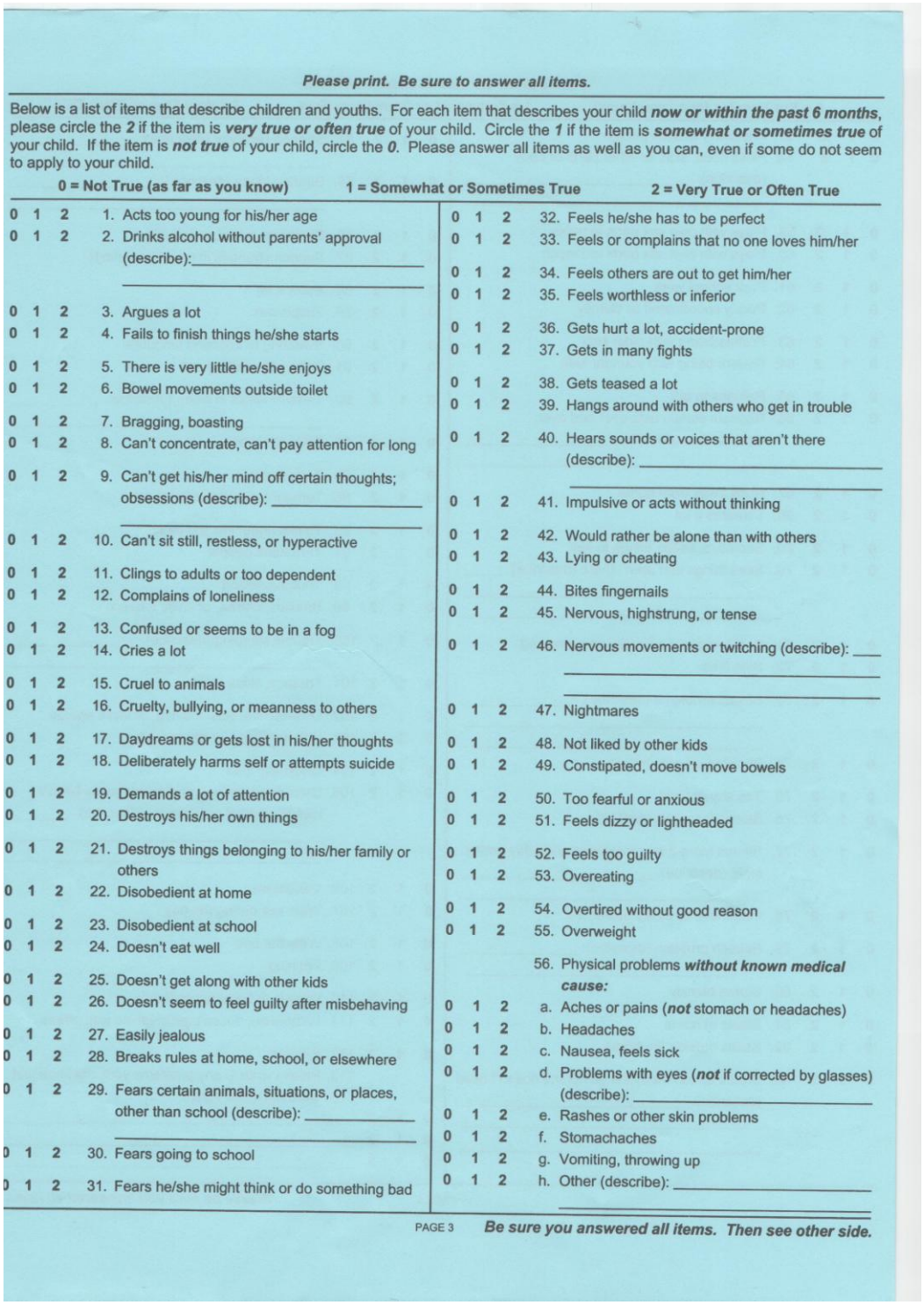
Does your child have any illness or disability (either physical or mental)? ❒ No ❒ Yes—please describe:

What concerns you most about your child?

Please describe the best things about your child.

PAGE 2

Be sure you answered all items.



Please print. Be sure to answer all items.

Below is a list of items that describe children and youths. For each item that describes your child ***now or within the past 6 months***, please circle the ***2*** if the item is ***very true or often true*** of your child. Circle the ***1*** if the item is ***somewhat or sometimes true*** of your child. If the item is ***not true*** of your child, circle the ***0***. Please answer all items as well as you can, even if some do not seem to apply to your child.

0 = Not True (as far as you know) **1 = Somewhat or Sometimes True** **2 = Very True or Often True**

0 1 2 1. Acts too young for his/her age
0 1 2 2. Drinks alcohol without parents' approval (describe):_____
0 1 2 3. Argues a lot
0 1 2 4. Fails to finish things he/she starts
0 1 2 5. There is very little he/she enjoys
0 1 2 6. Bowel movements outside toilet
0 1 2 7. Bragging, boasting
0 1 2 8. Can't concentrate, can't pay attention for long
0 1 2 9. Can't get his/her mind off certain thoughts; obsessions (describe): _____
0 1 2 10. Can't sit still, restless, or hyperactive
0 1 2 11. Clings to adults or too dependent
0 1 2 12. Complains of loneliness
0 1 2 13. Confused or seems to be in a fog
0 1 2 14. Cries a lot
0 1 2 15. Cruel to animals
0 1 2 16. Cruelty, bullying, or meanness to others
0 1 2 17. Daydreams or gets lost in his/her thoughts
0 1 2 18. Deliberately harms self or attempts suicide
0 1 2 19. Demands a lot of attention
0 1 2 20. Destroys his/her own things
0 1 2 21. Destroys things belonging to his/her family or others
0 1 2 22. Disobedient at home
0 1 2 23. Disobedient at school
0 1 2 24. Doesn't eat well
0 1 2 25. Doesn't get along with other kids
0 1 2 26. Doesn't seem to feel guilty after misbehaving
0 1 2 27. Easily jealous
0 1 2 28. Breaks rules at home, school, or elsewhere
0 1 2 29. Fears certain animals, situations, or places, other than school (describe): _____
0 1 2 30. Fears going to school
0 1 2 31. Fears he/she might think or do something bad
0 1 2 32. Feels he/she has to be perfect
0 1 2 33. Feels or complains that no one loves him/her
0 1 2 34. Feels others are out to get him/her
0 1 2 35. Feels worthless or inferior
0 1 2 36. Gets hurt a lot, accident-prone
0 1 2 37. Gets in many fights
0 1 2 38. Gets teased a lot
0 1 2 39. Hangs around with others who get in trouble
0 1 2 40. Hears sounds or voices that aren't there (describe): _____
0 1 2 41. Impulsive or acts without thinking
0 1 2 42. Would rather be alone than with others
0 1 2 43. Lying or cheating
0 1 2 44. Bites fingernails
0 1 2 45. Nervous, highstrung, or tense
0 1 2 46. Nervous movements or twitching (describe): _____
0 1 2 47. Nightmares
0 1 2 48. Not liked by other kids
0 1 2 49. Constipated, doesn't move bowels
0 1 2 50. Too fearful or anxious
0 1 2 51. Feels dizzy or lightheaded
0 1 2 52. Feels too guilty
0 1 2 53. Overeating
0 1 2 54. Overtired without good reason
0 1 2 55. Overweight
56. Physical problems ***without known medical cause:***
0 1 2 a. Aches or pains (***not*** stomach or headaches)
0 1 2 b. Headaches
0 1 2 c. Nausea, feels sick
0 1 2 d. Problems with eyes (***not*** if corrected by glasses) (describe): _____
0 1 2 e. Rashes or other skin problems
0 1 2 f. Stomachaches
0 1 2 g. Vomiting, throwing up
0 1 2 h. Other (describe): _____

PAGE 3 ***Be sure you answered all items. Then see other side.***

Author: Shashi Singh

Please print. Be sure to answer all items.

0 = Not True (as far as you know) **1 = Somewhat or Sometimes True** **2 = Very True or Often True**

0 1 2 57. Physically attacks people
0 1 2 58. Picks nose, skin, or other parts of body (describe): _____
_____
0 1 2 59. Plays with own sex parts in public
0 1 2 60. Plays with own sex parts too much
0 1 2 61. Poor school work
0 1 2 62. Poorly coordinated or clumsy
0 1 2 63. Prefers being with older kids
0 1 2 64. Prefers being with younger kids
0 1 2 65. Refuses to talk
0 1 2 66. Repeats certain acts over and over; compulsions (describe): _____
_____
0 1 2 67. Runs away from home
0 1 2 68. Screams a lot
0 1 2 69. Secretive, keeps things to self
0 1 2 70. Sees things that aren't there (describe): _____
_____
_____
0 1 2 71. Self-conscious or easily embarrassed
0 1 2 72. Sets fires
0 1 2 73. Sexual problems (describe): _____
_____
_____
0 1 2 74. Showing off or clowning
0 1 2 75. Too shy or timid
0 1 2 76. Sleeps less than most kids
0 1 2 77. Sleeps more than most kids during day and/or night (describe): _____
_____
0 1 2 78. Inattentive or easily distracted
0 1 2 79. Speech problem (describe): _____
_____
0 1 2 80. Stares blankly
0 1 2 81. Steals at home
0 1 2 82. Steals outside the home
0 1 2 83. Stores up too many things he/she doesn't need (describe): _____
_____
_____
0 1 2 84. Strange behavior (describe): _____
_____
0 1 2 85. Strange ideas (describe): _____
_____
0 1 2 86. Stubborn, sullen, or irritable
0 1 2 87. Sudden changes in mood or feelings
0 1 2 88. Sulks a lot
0 1 2 89. Suspicious
0 1 2 90. Swearing or obscene language
0 1 2 91. Talks about killing self
0 1 2 92. Talks or walks in sleep (describe): _____
_____
0 1 2 93. Talks too much
0 1 2 94. Teases a lot
0 1 2 95. Temper tantrums or hot temper
0 1 2 96. Thinks about sex too much
0 1 2 97. Threatens people
0 1 2 98. Thumb-sucking
0 1 2 99. Smokes, chews, or sniffs tobacco
0 1 2 100. Trouble sleeping (describe): _____
_____
0 1 2 101. Truancy, skips school
0 1 2 102. Underactive, slow moving, or lacks energy
0 1 2 103. Unhappy, sad, or depressed
0 1 2 104. Unusually loud
0 1 2 105. Uses drugs for nonmedical purposes (***don't*** include alcohol or tobacco) (describe): _____
_____
_____
0 1 2 106. Vandalism
0 1 2 107. Wets self during the day
0 1 2 108. Wets the bed
0 1 2 109. Whining
0 1 2 110. Wishes to be of opposite sex
0 1 2 111. Withdrawn, doesn't get involved with others
0 1 2 112. Worries
113. Please write in any problems your child has that were not listed above:
0 1 2 _____
0 1 2 _____
0 1 2 _____

Please be sure you answered all items.

Appendix 5.1.9

The International Classification of Headache Disorders

Second Edition

(ICHD-II)

1. MIGRAINE

- 1.1 Migraine without aura
- 1.2 Migraine with aura
  - 1.2.1 Typical aura with migraine headache
  - 1.2.2 Typical aura with non-migraine headache
  - 1.2.3 Typical aura without headache
  - 1.2.4 Familial hemiplegic migraine (FHM)
  - 1.2.5 Sporadic hemiplegic migraine
  - 1.2.6 Basilar-type migraine
- 1.3 Childhood periodic syndromes that are commonly precursors of migraine
  - 1.3.1 Cyclical vomiting
  - 1.3.2 Abdominal migraine
  - 1.3.3 Benign paroxysmal vertigo of childhood
- 1.4 Retinal migraine
- 1.5 Complications of migraine
  - 1.5.1 Chronic migraine
  - 1.5.2 Status migrainosus
  - 1.5.3 Persistent aura without infarction
  - 1.5.4 Migrainous infarction
  - 1.5.5 Migraine-triggered seizures
- 1.6 Probable migraine
  - 1.6.1 Probable migraine without aura
  - 1.6.2 Probable migraine with aura
  - 1.6.5 Probable chronic migraine

Coded elsewhere:

Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded according to the disorder.

General comment

Primary or secondary headache or both?

When a headache with migraine characteristics occurs for the first time in close temporal relation to another disorder that is a known cause of headache, it is coded according to the causative disorder as a secondary headache. When pre-existing migraine is made worse in close temporal relation to another disorder that is a known cause of headache, there are two possibilities, and judgment is required. The patient can either be given only the migraine diagnosis or be given both the migraine diagnosis and a secondary headache diagnosis according to the other disorder. Factors that support adding the latter diagnosis are: a very close temporal relation to the disorder, a marked worsening of the migraine, very good evidence that the disorder can cause or aggravate migraine, and improvement or resolution of migraine after relief from the disorder.

Introduction

Migraine is a common disabling primary headache disorder. Epidemiological studies have documented its high prevalence and high socio-economic and personal impacts. It is now ranked by the World Health Organization as number 19 among all diseases world-wide causing disability.

Migraine can be divided into two major sub-types. 1.1 *Migraine without aura* is a clinical syndrome characterised by headache with specific features and associated symptoms. 1.2 *Migraine with aura* is primarily characterised by the focal neurological symptoms that usually precede or sometimes accompany the headache. Some patients also experience a premonitory phase, occurring hours or days before the headache, and a headache resolution phase. Premonitory and resolution symptoms include hyperactivity, hypoactivity, depression, craving for particular foods, repetitive yawning and other less typical symptoms reported by some patients.

When a patient fulfils criteria for more than one subtype of migraine, all subtypes should be diagnosed and coded. For example, a patient who has frequent attacks with aura but also some attacks without aura should be coded as 1.2 *Migraine with aura* and 1.1 *Migraine without aura*.

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 attacks[1] 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 quality[7]
    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 phonophobia[8]
E. Not attributed to another disorder[9]

Notes:

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*.

When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.

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).

When attacks occur on ≥15 days/month for >3 months, code as 1.1 *Migraine without aura* and as 1.5.1 *Chronic migraine*.

Migraine headache is commonly bilateral in young children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.

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.

Pulsating means throbbing or varying with the heartbeat.

In young children, photophobia and phonophobia may be inferred from their behaviour.

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 oligaemia 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 disorder[1]

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:

fully reversible visual symptoms including positive features (*eg*, flickering lights, spots or lines) and/or negative features (*ie*, loss of vision)

fully reversible sensory symptoms including positive features (*ie*, pins and needles) and/or negative features (*ie*, numbness)

fully reversible dysphasic speech disturbance

C. At least two of the following:
   1. homonymous visual symptoms[1] 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 disorder[2]

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.

1.2.2 Typical aura with non-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 that does not fulfil 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 symptoms[1] 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 that does not fulfil criteria B-D for 1.1 *Migraine without aura* begins during the aura or follows aura within 60 minutes
E. Not attributed to another disorder[2]

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.

Comment:

In the absence of headache fulfilling criteria for 1.1 *Migraine without aura*, precise diagnosis of aura and its distinction from mimics that may signal serious disease (*eg*, transient ischaemic attack) become much more important.

1.2.3 Typical aura without headache

Description:

Typical aura consisting of visual and/or sensory symptoms with or without 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 not associated with headache.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B–D

B. Aura consisting of at least one of the following, with or without speech disturbance 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)

C. At least two of the following:
   1. homonymous visual symptoms[1] 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 does not occur during aura nor follow aura within 60 minutes

E. Not attributed to another disorder[2]

Notes:

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:

In some patients a typical aura is always followed by migraine headache, but many patients have, in addition, attacks with aura followed by non-migraine headache or even without headache. A small number of patients have 1.2.3 *Typical aura without headache* exclusively. More commonly, as patients with 1.2.1 *Typical aura with migraine headache* become older, their headache may lose migraine characteristics or disappear completely even though auras continue. Some individuals, primarily males, have 1.2.3 *Typical aura without headache* from onset.

In the absence of headache fulfilling criteria for 1.1 *Migraine without aura*, precise diagnosis of aura and its distinction from mimics that may signal serious disease (*eg*, transient ischaemic attack) become much more important. This distinction may require investigation. Especially if aura begins after age 40, if negative features (*eg*, hemianopia) are predominant, or if aura is prolonged or very short, other causes should be ruled out.

1.2.4 Familial hemiplegic migraine (FHM)

Description:

Migraine with aura including motor weakness and at least one first- or second-degree relative has migraine aura including motor weakness.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria B and C

B. Aura consisting of fully reversible motor weakness and at least one of the following:
   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. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
   2. each aura symptom lasts ≥5 minutes and <24 hours
   3. headache fulfilling criteria B-D for 1.1 *Migraine without aura* begins during the aura or follows onset of aura within 60 minutes

D. At least one first- or second-degree relative has had attacks fulfilling these criteria A-E

E. Not attributed to another disorder[1]

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:

It may be difficult to distinguish weakness from sensory loss.

New genetic data have allowed a more precise definition of FHM than previously. Specific genetic subtypes of 1.2.4 *Familial hemiplegic migraine* have been identified: in FHM1 there are mutations in the CACNA1A gene on chromosome 19, and in FHM2 mutations occur in

the ATP1A2 gene on chromosome 1. If genetic testing is done, the genetic subtype should be specified parenthetically.
It has been shown that FHM1 very often has basilar-type symptoms in addition to the typical aura symptoms and that headache is virtually always present. During FHM1 attacks, disturbances of consciousness (sometimes including coma), fever, CSF pleocytosis and confusion can occur. FHM1 attacks can be triggered by (mild) head trauma. In approximately 50% of FHM1 families, chronic progressive cerebellar ataxia occurs independently of the migraine attacks.
FHM is very often mistaken for epilepsy, and (unsuccessfully) treated as such.

1.2.5 Sporadic hemiplegic migraine

***Description*:**

Migraine with aura including motor weakness but no first- or second-degree relative has aura including motor weakness.

Diagnostic criteria:

A. At least 2 attacks fulfilling criteria Band C
B. Aura consisting of fully reversible motor weakness and at least one of the following:
    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. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
    2. each aura symptom lasts ≥5 minutes and <24 hours
    3. headache fulfilling criteria B-D for 1.1 *Migraine without aura* begins during the aura or follows onset of aura within 60 minutes
D. No first- or second-degree relative has attacks fulfilling these criteria A-E
E. Not attributed to another disorder[1]

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*:**
Epidemiological studies have shown that sporadic cases occur with approximately the same prevalence as familial cases. The attacks have the same clinical characteristics as those in 1.2.4 *Familial hemiplegic migraine*.
Sporadic cases always require neuroimaging and other tests to rule out other cause. A lumbar puncture is also necessary to rule out pseudomigraine with temporary neurological symptoms and lymphocytic pleocytosis. This condition is more prevalent in males and often associated with transient hemiparesis and aphasia.

1.2.6 Basilar-type migraine

Previously used terms:
Basilar artery migraine, basilar migraine

Description:
Migraine with aura symptoms clearly originating from the brainstem and/or from both hemispheres simultaneously affected, but no motor weakness.

Diagnostic criteria:
A. At least 2 attacks fulfilling criteria B-D
B. Aura consisting of at least two of the following fully reversible symptoms, but no motor weakness:
    1. dysarthria
    2. vertigo
    3. tinnitus
    4. hypacusia
    5. diplopia
    6. visual symptoms simultaneously in both temporal and nasal fields of both eyes
    7. ataxia
    8. decreased level of consciousness
    9. simultaneously bilateral paraesthesias
C. At least one of the following:
    1. at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
    2. each aura 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 disorder[1]

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:

Basilar-type attacks are mostly seen in young adults. Many patients who have basilar-type attacks also report attacks with typical aura (code for both disorders).

If motor weakness is present, code as 1.2.4 *Familial hemiplegic migraine* or 1.2.5 *Sporadic hemiplegic migraine*. Patients with 1.2.4 *Familial hemiplegic migraine* have basilar-type symptoms in 60% of cases. Therefore, 1.2.6 *Basilar-type migraine* should be diagnosed only when no motor weakness occurs.

Many of the symptoms listed under criterion B are subject to misinterpretation as they may occur with anxiety and hyperventilation.

Originally the terms *basilar artery migraine* or *basilar migraine* were used but, since involvement of the basilar artery territory is uncertain (*ie*, the disturbance may be bihemispheric), the term *basilar-type migraine* is preferred.

1.3 Childhood periodic syndromes that are commonly precursors of migraine

1.3.1 Cyclical vomiting

Description:

Recurrent episodic attacks, usually stereotypical in the individual patient, of vomiting and intense nausea. Attacks are associated with pallor and lethargy. There is complete resolution of symptoms between attacks.

Diagnostic criteria:

A. At least 5 attacks fulfilling criteria Band C
B. Episodic attacks, stereotypical in the individual patient, of intense nausea and vomiting lasting from 1 hour to 5 days
C. Vomiting during attacks occurs at least 4 times/hour for at least 1 hour
D. Symptom-free between attacks
E. Not attributed to another disorder[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal disease.

Comment:

Cyclical vomiting is a self-limiting episodic condition of childhood, with periods of complete normality between episodes. This disorder was not included as a childhood periodic syndrome in the first edition of *The International Classification of Headache Disorders*. The clinical features of this syndrome resemble those found in association with migraine headaches, and multiple threads of research over the last years have suggested that cyclical vomiting is a condition related to migraine.

1.3.2 Abdominal migraine

Description:

An idiopathic recurrent disorder seen mainly in children and characterised by episodic midline abdominal pain manifesting in attacks lasting 1-72 hours with normality between episodes. The pain is of moderate to severe intensity and associated with vasomotor symptoms, nausea and vomiting.

Diagnostic criteria:

A. At least 5 attacks fulfilling criteria B-D
B. Attacks of abdominal pain lasting 1-72 hours (untreated or unsuccessfully treated)
C. Abdominal pain has all of the following characteristics:
    1. midline location, periumbilical or poorly localised
    2. dull or “just sore” quality
    3. moderate or severe intensity
D. During abdominal pain at least 2 of the following:
    1. anorexia
    2. nausea
    3. vomiting
    4. pallor
E. Not attributed to another disorder[1]

Note:

1. In particular, history and physical examination do not show signs of gastrointestinal or renal disease or such disease has been ruled out by appropriate investigations.

Comments:
Pain is severe enough to interfere with normal daily activities.
Children may find it difficult to distinguish anorexia from nausea. The pallor is often accompanied by dark shadows under the eyes. In a few patients flushing is the predominant vasomotor phenomenon.
Most children with abdominal migraine will develop migraine headache later in life.

1.3.3 Benign paroxysmal vertigo of childhood

Description:
This probably heterogeneous disorder is characterised by recurrent brief episodic attacks of vertigo occurring without warning and resolving spontaneously in otherwise healthy children.

Diagnostic criteria:
A. At least 5 attacks fulfilling criterion B
B. Multiple episodes of severe vertigo[1], occurring without warning and resolving spontaneously after minutes to hours
C. Normal neurological examination; audiometric and vestibular functions between attacks
D. Normal electroencephalogram

Note:
1. Often associated with nystagmus or vomiting; unilateral throbbing headache may occur in some attacks.

1.4 Retinal migraine

Description:
Repeated attacks of monocular visual disturbance, including scintillations, scotomata or blindness, associated with migraine headache.

Diagnostic criteria:
A. At least 2 attacks fulfilling criteria B and C
B. Fully reversible monocular positive and/or negative visual phenomena (*eg*, scintillations, scotomata or blindness) confirmed by examination during an attack or (after proper instruction) by the patient's drawing of a monocular field defect during an attack
C. Headache fulfilling criteria B-D for 1.1 *Migraine without aura* begins during the visual symptoms or follows them within 60 minutes

D. Normal ophthalmological examination between attacks
E. Not attributed to another disorder[1]

Note:

1. Appropriate investigations exclude other causes of transient monocular blindness.

Comment:

Some patients who complain of monocular visual disturbance in fact have hemianopia. Some cases without headache have been reported, but their migrainous nature cannot be ascertained. Other causes of transient monocular blindness (*amaurosis fugax*), such as optic neuropathy or carotid dissection, must be excluded.

1.5 Complications of migraine

Comment:

Code separately for both the antecedent migraine subtype and for the complication.

1.5.1 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 8.2.7 *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 8.2.7 *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.

1.5.2 Status migrainosus

Description:

A debilitating migraine attack lasting for more than 72 hours.

Diagnostic criteria:

A. The present attack in a patient with 1.1 *Migraine without aura* is typical of previous attacks except for its duration
B. Headache has both of the following features:
   unremitting for >72 hours
   severe intensity
C. Not attributed to another disorder

Comment:

Interruption during sleep is disregarded. Short-lasting relief due to medication is also disregarded. Status may often be caused by medication overuse and should be coded accordingly. Non-debilitating attacks lasting >72 hours but otherwise meeting these criteria are coded as 1.6.1 *Probable migraine without aura*.

1.5.3 Persistent aura without infarction

Description:

Aura symptoms persist for more than 1 week without radiographic evidence of infarction.

Diagnostic criteria:

A. The present attack in a patient with 1.2 *Migraine with aura* is typical of previous attacks except that one or more aura symptoms persists for >1 week
B. Not attributed to another disorder

Comments:
Persisting aura symptoms are rare but well documented. They are often bilateral and may last for months or years. Reliably effective treatment is not known though acetazolamide and valproic acid have helped in a few cases.
Exclude posterior leukoencephalopathy by diffusion MRI among other things. Exclude 1.5.4 *Migrainous infarction* by MRI.

1.5.4 Migrainous infarction

Description:
One or more migrainous aura symptoms associated with an ischaemic brain lesion in appropriate territory demonstrated by neuroimaging.

Diagnostic criteria:
A. The present attack in a patient with 1.2 *Migraine with aura* is typical of previous attacks except that one or more aura symptoms persists for >60 minutes
B. Neuroimaging demonstrates ischaemic infarction in a relevant area
C. Not attributed to another disorder

Comments:
Ischaemic stroke in a migraine sufferer may be categorised as cerebral infarction of other cause coexisting with migraine, cerebral infarction of other cause presenting with symptoms resembling migraine with aura, or cerebral infarction occurring during the course of a typical migraine with aura attack. Only the last fulfils criteria for 1.5.4 *Migrainous infarction*.
Increased risk for stroke in migraine patients has been demonstrated in women under age 45 in several studies. Evidence for an association between migraine and stroke in older women and in men is inconsistent.

1.5.5 Migraine-triggered seizure

Description:
A seizure triggered by a migraine aura.

Diagnostic criteria:
A. Migraine fulfilling criteria for 1.2 *Migraine with aura*
B. A seizure fulfilling diagnostic criteria for one type of epileptic attack occurs during or within 1 hour after a migraine aura

Comment:
Migraine and epilepsy are prototypical examples of paroxysmal brain disorders. While migraine-like headaches are quite frequently seen in the postictal period, sometimes a

seizure occurs during or following a migraine attack. This phenomenon, sometimes referred to as *migralepsy*, has been described in patients with migraine with aura.

1.6 Probable migraine

Previously used terms:

Migrainous disorder

Coded elsewhere:

Migraine-like headache secondary to another disorder (*symptomatic migraine*) is coded according to that disorder.

Description:

Attacks and/or headache missing one of the features needed to fulfil all criteria for a disorder coded above (1.6.3 *Probable childhood periodic syndromes that are commonly precursors of migraine* and 1.6.4 *Probable retinal migraine* are not currently recognised).

1.6.1 Probable migraine without aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.1 *Migraine without aura*
B. Not attributed to another disorder

Comment:

Do not code as 1.6.1 *Probable migraine without aura* if the patient fulfils the criteria for 1.5.1 *Chronic migraine* or 1.5.2 *Status migrainosus*.

1.6.2 Probable migraine with aura

Diagnostic criteria:

A. Attacks fulfilling all but one of criteria A-D for 1.2 *Migraine with aura* or any of its subforms
B. Not attributed to another disorder

1.6.5 Probable chronic migraine

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] but there is, or has been within the last 2 months, medication overuse fulfilling criterion B for any of the subforms of 8.2 *Medication-overuse headache*

Note:

1. History and physical and neurological examinations do not suggest any of the disorders listed in groups 5-12 (other than 8.2 *Medication-overuse headache*), 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.

Aggravating factors

Migraine may be aggravated by a number of factors. That is, in a person who already meets criteria for migraine, particular factors may be associated with a relatively long-term (usually weeks to months) increase in the severity or frequency of attacks. Examples of commonly-reported aggravating factors include: psychosocial stress, frequent intake of alcoholic beverages, other environmental factors.

Trigger factors (precipitating factors)

Trigger factors increase the probability of a migraine attack in the short term (usually <48 hours) in a person with migraine. Though some trigger factors have been reasonably well studied epidemiologically (*eg*, menstruation) or in clinical trials (*eg*, chocolate, aspartame), causal attribution in individual patients may be difficult.

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