

**BIOPSYCHOSOCIAL CORRELATES OF HEALTH-RELATED
QUALITY OF LIFE IN MIGRAINE WITHOUT AURA**

by

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submitted in accordance with the requirements
for the degree of

DOCTOR OF PHILOSOPHY

In the subject

PSYCHOLOGY

at the

UNIVERSITY OF SOUTH AFRICA

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NOVEMBER 2016

Declaration

I hereby declare that this thesis “Biopsychosocial correlates of health-related quality of life in migraine without aura” is my own work, unless otherwise stated. All the sources that I have used or quoted have been indicated and acknowledged by means of complete references.

Student number: 54671051

A handwritten signature in black ink, appearing to read 'Jacobs', written on a light-colored rectangular background.

30 June 2016

Signature

Date

Acknowledgements

This PhD journey has been gruelling and I would not have been able to finish it without the various forms of support I received. I therefore have a number of people that I need to thank for walking various parts of the journey with me. Though the list seems extensive, it is probably not complete...

Thank you to the Creator for the opportunity to improve myself and for the wonderful people that helped make it possible.

Academic and financial support

It took me almost two years to find a promoter and I am infinitely grateful to Professors Elander and Rees for taking the journey with me. I also thank Professor Michael Pepper who stood by me in the first few steps of the journey.

I acknowledge the National Research Foundation for funding my PhD through the Thuthuka Programme. I am grateful to Professor Rhena Delpont who helped me to apply for the NRF funds, along with Christiaan Labuschagne who offered the initial advice on gene sequencing. I am incredibly thankful to Mrs Hanneke Nieuwoudt who kept the books for my grant and always helped when I was confused or frustrated; and Ms Kentse Mabalane and Mrs Bettie de Beer of the NRF for their advice on funding.

Thank you, Charles Wairuri from Whitehead Scientific for always answering my questions.

I am sincerely grateful to Dr Lisa Zimmerman for helping with my conceptual clarity and Dr Dion van Zyl for statistical clarity.

Heartfelt thanks are also in order for my statistician, Dr Mardé Booyse, for her patience and help.

Thank you, Dr André Stander for letting me utilise space in your laboratory. This was crucial to my study. Thank you also for guiding me through the qPCR process – you are a very patient gentleman and lecturer.

The participants

I am grateful to all the participants: You sacrificed time and blood for this – thank you.

Moral support

I am incredibly grateful to my super supporters: Angelo, Boshadi, Christine L., Ed, Liz, Martin, Nico, Nikki, Puleng and Vanessa. Thank you for listening to my woes and helping me keep my spirits up. It meant more than I can express.

Thank you also to all my family who helped out when I had to work. I am especially grateful to Anna, Carina and Ingrid, Cass, Christine M., Cecilia, Christopher, Ian and Jaqui, Jacky, Jutta, Melinda and Shainaaz for making time for last-minute visits, babysitting and play-dates!

Technical support

My gratitude is extended to Benita Colmanet for organising all the phlebotomy. Thank you to Sr Jean-Louise Brits for being our traveling phlebotomist. I acknowledge with much appreciation the Ampath teams at Zuid-Afrikaans Hospital, Linksfield Hospital, Morningside Clinic, Rosebank Clinic and Flora Clinic for collecting the samples and running the panel of tests. In particular I want to thank Marisa, Errol, Kagisho, Carlos and Beverley for caring about my study.

I am incredibly appreciative of the people that helped me to advertise my study: Angela Cogzell and friends and a number of colleagues who were willing to lend a hand. There were also a few organisations that allowed me to advertise. Though I can't name you, I remain grateful.

The gentlemen at the Agricultural Research Council's OVI were wonderful and I am grateful for your expert help, Dr Shaun Reeksting and Dr Liberty Sibanda.

Jaqueline Harvey: Thank you for all the competent help with the laboratory work and the encouragement when it was hard going. I would not have been able to finish this year if you had not been there – even on weekends!

Mentorship

Annelies Cramer: Many years ago you inspired me to take up a career in neuropsychology. You continue to be a mentor and I feel blessed that our paths crossed.

Nafisa Cassimjee: Thank you for believing in me enough to send me to Canada to be inspired.

To my longstanding friend and one of the most courageous researchers I know, Dr Alida Koorts: I value your friendship and the way you selflessly share your expertise, your

laboratory, your pipettes and your time. Thank you for encouraging and inspiring me over the years.

Inspiration

During this journey I have continually been grateful for the privilege of my education. That was a gift of untold value from my parents. My mother, Iris, died in 2011 and my father, Krish, died while I was completing this thesis journey in 2016. May they both rest in peace.

I also acknowledge the women in my family who believed in education though they were not able to receive it to the level they may have wanted.

Finally, warm and infinite thanks go to Liz, Grace, Cecilia and Christopher for the constancy of their love.

This thesis is dedicated to three of the most
influential women in my life:

For Liz, whose courage astounds me...

For Grace, who makes sunshine wherever she goes...

And especially for my mother, Iris Beryl Govender, who
attended every one of my graduations, but will not be in the
audience for this one...

Abstract

Migraine - with or without aura - is an enervating primary headache disorder that represents a heavy economic and social burden. The health-related quality of life of migraineurs is poor. The aim of this research was to investigate the health-related quality of life of migraine without aura sufferers.

As the thesis was approached from a biopsychosocial perspective, potential determinants were chosen for investigation from the molecular, individual, interpersonal and wider societal levels. The research was executed in two phases: Phase 1 data ($N = 341$) were gathered using a survey of health-related quality of life (Short Form 6), temperament (the Tridimensional Personality Questionnaire), catastrophizing as a pain coping strategy (the four-item Pain Coping Scale) and the amount of perceived social support (the six-item Social Support Questionnaire). For phase 2, participants were requested to provide blood specimens for ELISA serum quantification of glutamate ($n = 66$) and gene expression analysis of the main glutamate transporter gene SLC1A2 on real-time reverse-transcription polymerase chain reaction ($n = 20$).

Of the 341 adult residents of Gauteng Province, South Africa that participated in the survey, 94 (28%) met the criteria for migraine without aura and a further 60 (18%) suffer from possible migraine without aura, using the International Classification of Headache Diagnosis (2nd edition) criteria. This indicates that migraine without aura is a significant burden for South Africa.

Health-related quality of life was significantly poorer for migraineurs versus those without migraine ($p < .001$), and is in fact comparable to that of liver transplant, cardiac bypass and elderly populations. This raises concerns about the severe burden of the disease on the mental and physical well-being of South African sufferers.

Investigation of the predictors of health-related quality of life yielded two significant variables when controlling for sex, head and neck injury and language - Harm Avoidance and

Catastrophizing. The regression model accounts for 29% of the variance in health-related quality of life. A reciprocal relationship likely exists between Harm Avoidance and Catastrophizing, in which a harm avoidant migraineur interprets the headache pain as a catastrophic event to be avoided – even at high cost to the self.

Though there have been calls for more biopsychosocial studies of migraine, this thesis did not find added understanding of health-related quality of life through the combination of biological and psychosocial data. The implication is that the role of glutamate in migraine without aura still requires further investigation. Further study is also required with regard to which biological factors may influence the sufferer's quality of life.

The thesis indicates a key role for psychological intervention in aiding migraineurs to live a life of quality. The inclusion of interventions for the psychological aspects of migraine may yield improved outcomes for patients. However, Gauteng residents suffering from MO are potentially unaware of their diagnosis and therefore of potential management for their disorder. Awareness around migraine needs to be the first step in limiting this disorder's devastating impact on individuals, their relationships and their potential to contribute meaningfully to society.

Key terms: health-related quality of life, biopsychosocial, glutamate, migraine without aura, pain coping, SLC1A2, temperament

List of abbreviations

CSD	Cortical spreading depression
DA	Dopamine
DTI	Diffusion tensor imaging
EAAT-2	Excitatory amino acid transporter
EDTA	Ethylenediaminetetraacetic acid
EEG	Electroencephalography
ELISA	Enzyme-linked immunosorbance assay
FHM	Familial hemiplaegic migraine
Glu	Glutamate
GWAS	Genome-wide association study
HA	Harm avoidance
HRQOL	Health-related quality of life
MA	Migraine with aura
MO	Migraine without aura
NA	Noradrenalin
NM	Non-migraineur(s)
NS	Novelty seeking
P	Perseverance
PET	Positron emission tomography
QOL	Quality of life
qPCR	Quantitative polymerase chain reaction
rCBF	Regional cerebral blood flow
RD	Reward dependence
RT ²	Real-time reverse transcription
Ser	Serotonin
SLC1A2	Solute-carrier family 1 glial high affinity glutamate transporter 2
SSQ	Social Support Questionnaire
SPECT	Single-photon emission computed tomography
TPQ	Tridimensional Personality Questionnaire

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Chapter 1: Introduction to the Study

This chapter introduces the thesis by providing the rationale and motivation for the research, while engaging in critical debate about the significance of such research within international and local contexts. The objectives of the thesis are laid out with reference to the aims and research questions in order to provide a clear map of how the work was conducted. The chapter concludes with an outline of the thesis chapters to help guide the reader through the work.

1.1 Health-Related Quality of Life in a Biopsychosocial Framework

The focus of this research was on health-related quality of life (HRQOL) in migraine without aura (MO). Specifically, a biopsychosocial framework was used to investigate the interactions between temperament, glutamate neurotransmission, pain coping, social support and, ultimately, how they may influence the MO sufferer's HRQOL.

The HRQOL concept is composed of physical, psychological and social components (Ferrans, 2005) that can be related to the biological and psychosocial contexts in which an individual exists (Kuehn & McClain, 1994). As such, HRQOL embodies Engel's (Engel, 1980) notions that an individual can be best understood in the context of the multiple systems in which she exists and that these systems are not isolated.

As a subjective construct HRQOL offers a unique opportunity for individuals to provide health representatives with their personal views of how their actual and ideal health compare (Cella, 1994). Such incorporation of the individual's (or patient's) view is also a central principle in the biopsychosocial framework (Engel, 1977; 1980).

The broad field of pain research has benefitted greatly from biopsychosocial approaches to research (Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Lumley et al., 2011), but it was only more recently that researchers began to call for more inclusion of a

biopsychosocial perspective specifically in headache research (Martin, 2007). Studies of how psychosocial difficulties contribute to migraine HRQOL are not common (Leonardi, Raggi, Bussone, & D'Amico, 2010; Raggi et al., 2012). Studies making use of a biopsychosocial perspective to guide our understanding of HRQOL in migraine are therefore also uncommon. The relative novelty of the study approach aside, in making use of the biopsychosocial perspective in exploring HRQOL in MO, this research has the potential to invite partnership between healthcare providers and MO sufferers in their systems as they tackle the challenges of this disorder (Borrell-Carrió, Suchman, & Epstein, 2004).

This thesis draws from knowledge and techniques not traditionally associated with psychological studies in South Africa, including genetics and physiology. Within the South African context (or any other developing context, perhaps), interdisciplinary research is still establishing itself as a valuable force in the knowledge economy (National Research Foundation, 2014).

Some of the difficulties in publishing interdisciplinary research has been presented by (Gajovic, 2015) and some of the practicalities of PhD-level interdisciplinary research is addressed by Sharp (2016). However, neither of these articles deals with the realities of a developing world context. Winberg, Barnes, Ncube, and Tshinu (2011) discuss the experiences of South African students conducting interdisciplinary research, though their work focuses on issues of the struggle for definition of the research. The structural challenges of such interdisciplinary work for South African PhD candidates are not addressed in these articles, though. These include matters of part-time registration being the only viable option for an estimated 80% of PhD candidates in South Africa (Dell, 2010) and the challenges of securing postgraduate supervision for interdisciplinary work Winberg et al. (2011). This thesis makes a significant contribution to South African research that will hopefully encourage other researchers to embark on interdisciplinary projects in the face of these challenges.

1.2 Problem Statement

Headaches are a major health concern around the globe (Stovner et al., 2007). The World Health Organisation estimates that 47% of adults (18-65 years of age) suffered a headache at least once in 2011 (World Health Organization, 2012). Although headaches are associated with substantial social and economic cost (Stovner et al., 2007; Wieser, Walliser, Womastek, & Kress, 2012), they are thought to be underdiagnosed and undertreated worldwide (World Health Organization, 2012). Migraine has become a “forgotten epidemic” (Diener, Steiner, & Tepper, 2006, p.433). Given the high prevalence and the burden of headaches, questions arise about how people may still experience a life of quality in spite of a headache; how they cope with the pain; and the factors that contribute positively and negatively to HRQOL of headache sufferers.

There are several subtypes of headache with divergent symptoms and aetiologies. The focus of this research has been narrowed to migraine without aura (MO), which is described in more detail in Chapter 2. Migraine is typified by severe pain (Villalón & Olesen, 2009; Wendt, Cady, Singer, & Peters, 2006) and is considered to be a chronic disorder with episodic manifestations (Aydemir, Ozkara, Unsal, & Canbeyli, 2011). The condition is diagnosed as chronic when headaches occur for 15 or more days of the month for a minimum of three months (Galletti, Cupini, Corbelli, Calabresi, & Sarchielli, 2009; Pompili et al., 2010). A more in-depth discussion of migraine is undertaken in the next chapter.

Though migraine may not decrease life expectancy (Magnusson & Becker, 2003), it has a profound impact on HRQOL (Bera, Goyal, Khandelwal, & Sood, 2014; Brna, Gordon, & Dooley, 2006; D’Amico, Grazi, Usai, Leonardi, & Raggi, 2013; D’Amico, Leonardi, Grazi, Curone, & Raggi, 2015; Dalhof & Dimenas, 1995; de Velasco & Gonzalez, 2003) and the importance of understanding what contributes to and detracts from HRQOL in MO is clear when one considers the poor reported health outcomes of migraineurs. For example, Aydemir et al.'s (2011) study using the Short-Form 36 (SF-36) questionnaire showed that

HRQOL is lower amongst migraine sufferers in comparison to healthy subjects and even to people diagnosed with epilepsy. Similarly, migraine patients have shown lower mean global scores on the Health Utilities Index (HUI) in comparison to patients visiting a rheumatoid arthritis clinic; and scores equal to those of a cross section of Type 2 diabetes patients (Brown et al., 2008). According to Dalhof and Dimenas (1995), poor HRQOL in migraineurs extends even into the periods between migraine attacks. Migraine is also the most frequently reported primary headache disorder amongst headache sufferers seeking treatment (Villalón & Olesen, 2009; Wendt, Cady, Singer, & Peters, 2006), with MO being the more frequently reported of the two migraine subtypes (Villalón & Olesen, 2009).

However, migraine is not simply an individual burden - it affects not only the sufferer, but has clear implications for the wider systems in which an individual is situated. The relatively few peer-reviewed articles that deal with the matter of interpersonal effects of migraine indicate that family relationships suffer under the strain of a partner / parent in pain: In a study of 350 migraine sufferers in the United States, Smith found that migraine sufferers felt that their headaches had significantly negative effects on family life and were a source of conflict, unhappiness and instability (Smith, 1998). In some cases migraine sufferers were perceived as not providing adequate care for their children as they often had to make alternate care arrangements or cancel outings because of their headaches. Migraine affected the frequency or quality of the sexual relationships between partners in 24% of the sample and in 5% of the cases, migraine was seen as a direct cause of divorce or separation of partners. In a later study of 100 partners of migraine sufferers in both the United Kingdom and the United States, partners indicated that the migraine sufferer would be a better partner were it not for the headaches (Lipton et al., 2003). The migraineurs concurred, indicating that their headaches interfered with their social and family life commitments and prevented them from planning ahead for fear of a migraine attack. Migraine sufferers also felt that their migraine made it more likely that they would argue with their children and their partners.

In the workplace migraine affects the quality of work. A study of labour cost in migraine sufferers in the United States ($N = 648$) showed that 50% of migraine sufferers missed an average of two days per month due to headaches and that even when they were at work their productivity was severely diminished when a headache struck (Osterhaus, Gutterman, & Plachetka, 1992). In a multinational study of 2670 migraine sufferers, it was estimated that productivity is diminished by 46% when sufferers work with a migraine and had to be away from work for 19.5 days a year because of their headaches (Gerth, Carides, Dasbach, Visser, & Santanello, 2001).

The socio-economic burden of migraine has also become clear in recent years. The peak incidence of migraine occurs between 25 and 44 years of age (Jette, Patten, & Williams, 2008), when economic and psychosocial productivity should be high (Brown et al., 2005). Migraine is associated with high costs in terms of treatment and lost productivity in European, North American and Asian populations (Lantéri-Minet et al., 2003; Lipton & Bigal, 2005; Rasmussen, Jensen, Schroll, & Olesen, 1995; Unger, 2006; Wang, 2003). In the United States these costs are estimated to be \$17 billion per annum (Norton, Asmundson, Norton, & Craig, 1999). The Eurolight Project calculates costs for migraine to be €11 billion per annum in Europe (accounting for 64% of the cost burden of all headaches examined) (Linde, 2006). Migraine is one of the diseases for which the cumulative indirect lifetime societal cost exceeds direct costs for medical care (Gurwitz & Diamond, 2007), making it a serious liability to society.

The severe liability created by migraine is compounded by a lack of cure. The management of the disorder can therefore benefit from critical examination of the aspects of the headache which impact the sufferers and the means by which they cope and function (Magnusson & Becker, 2003) - essentially, an improved understanding of predictors of their HRQOL.

1.3 Motivation for the Study

With these poor outcomes in mind, HRQOL research in migraine becomes foregrounded as a theoretically significant means of moving from diagnosis to improved care and intervention in headaches. Unfortunately, there is currently a gap in South African literature regarding a number of aspects of migraine – including HRQOL. Some peer-reviewed prevalence statistics are available for Benin, Nigeria, Ethiopia, Tanzania and Zimbabwe (Adoukonou, Houinato, & Kankouan, 2009; Houinato et al., 2010; Leonardi, Steiner, Scher, & Lipton, 2005; Mengistu & Alemayehu, 2013; Osuntokun et al., 1992), but South Africa has not been closely examined and information regarding the number of migraine cases, demographics of migraine sufferers, impact of the pain, and so forth, has not been collated for this country. However, a South African headache expert, Elliot Shevel, has been quoted as saying that South African prevalence is unlikely to differ from the global 10% estimate (Green, 2015). Only two studies could be identified that examine migraine prevalence in South Africa. Both studies explored the occurrence of migraine amongst South African hazardous drinkers. The prevalence of the disorder was very high in both studies (14-30%), but given the restricted sample population, it would be premature to extrapolate these findings to the general population (Mertens et al., 2010; Pengpid, Peltzer, & Van der Heever, 2011).

Without comprehensive peer-reviewed data on even the most basic questions about migraine in South Africa, it is difficult to imagine a clear and precise strategy toward understanding the disease and improving interventions. Information regarding the general characteristics of migraine sufferers and their HRQOL is needed to bridge the gap between bench and bedside. There is therefore a strong need for systematic, inter-disciplinary approaches to migraine research in South Africa and indeed, on the majority of the African continent. In order to start addressing the gap in the literature, this study began with an exploration of the demographics, HRQOL and psychological functioning of MO sufferers

living in the Gauteng Province, South Africa. The focus of the work shifted from a general overview of MO to concentrate on factors that may help us understand the level of HRQOL in MO.

The distinction between the two major subtypes of migraine with aura (MA) and MO was emphasized in this study because of the considerable differences in prevalence, prodromal and attack features as well as clinical data, which indicate that MA and MO are separate disorders or, at the very least, disorders on two different ends of a spectrum (Christensen, Le, Kirchmann, & Olesen, 2012; Ludvigsson, Hesdorffer, Olafsson, Kjartansson, & Hauser, 2006; Russell, Rasmussen, Fenger, & Olesen, 1996; Russell, Ulrich, Gervil, & Olesen, 2002). The choice to investigate MO instead of MA was based on the following: MO is more frequently reported than MA (Villalón & Olesen, 2009). This research could therefore assist in managing treatment for the majority of migraineurs. Using such a focused approach could also aid in the understanding of biological markers and psychosocial assets and liabilities in MO, which is important for the planning of interventions for MO sufferers and others affected by the disorder. For example, variations in neurotransmission that are associated with significant differences in HRQOL may be useful in understanding differences in coping and temperament in MO. Understanding the neurotransmitter, temperament and coping interaction may hold particular significance for isolating psychological assets for specific pain management interventions (Esposito et al., 2013; Friedman, 1968) or understanding processes such as the transformation of migraine to chronic daily headache through the development of medication overuse headache (Matsumoto et al., 2007). Moreover, the symptom of aura in MA would have introduced a further confounding variable; the heterogeneity of those aura experiences complicating the study further. It was assumed that the prioritised focus on MO over MA would decrease the likelihood of within-group heterogeneity, thereby increasing the research manageability, while allowing for in-depth examination of the impact of MO pain on the migraineur' s HRQOL.

1.4 Aims, Objectives and Research Questions

In this thesis it was the possibility that the MO individual's HRQOL can be predicted by certain biopsychosocial factors was explored. These factors were: Temperament, neurotransmission profile, coping mechanisms that the individual employs to deal with the pain of MO headache and levels of perceived social support. Temperament is the automatic emotional response to situations (Boz et al., 2004). It is key to the processes of emotional reactivity and regulation (Henderson & Wachs, 2007), hence, it is a determinant of the significance one attaches to events, emotional reactions and habits (Boz et al., 2004). It is therefore not surprising that temperament has been associated with aspects of cognition and emotion, including coping (Gentzler, Kerns, & Keener, 2009; Marais & Stuart, 2006) and perceived social support (Kitamura, Kijima, Watanabe, Takezaki, & Tanaka, 1999). In addition, specific temperament dimensions have been significantly associated with various headache disorders, including migraine (Boz et al., 2004; Mongini, Fassino, et al., 2005; Sánchez-Román et al., 2007). The research approached temperament from the perspective of Cloninger's Psychobiological Theory of Personality, which holds that neurotransmitters underpin temperament (Celikel et al., 2009; Gillespie, Cloninger, Heath, & Martin, 2003). The neurotransmitter, glutamate, while thought to play a role in temperament (Matsumoto et al., 2007), has also been significantly associated with MO (Christensen et al., 2012; Lighthart et al., 2011). Thus, HRQOL determinants put forward in this research were derived from molecular, individual and interpersonal levels, with inclusion of wider society factors (lifestyle habits) in the analysis.

There are two disclaimers that should be highlighted, though: Although this research does not investigate such factors, it is acknowledged that environmental factors do influence both neurotransmission and temperament - the emerging research in the field of epigenetics (e.g. Wills, Sandy, & Yaeger, 2000) is testament to the influence of the environment and life events on the biological self (Slavich & Cole, 2013). However, exploration of MO and its

associated HRQOL has been limited in this thesis to allow improved manageability. The feedback from the environment and how this may alter temperament at behavioural and genomic levels were therefore considered outside the scope of this investigation. Furthermore, the question of MO aetiology is not investigated since an understanding of what causes MO was not the focus of this research. Rather, the emphasis of the work is on how the subjective experience of HRQOL in MO is constructed through a combination of biological and psychosocial events.

The aims of the study were to:

1. Compare the HRQOL of MO sufferers and participants not suffering from MO
2. Explore the association between temperament and pain coping in MO
3. Examine how neurotransmission, temperament, pain coping, perceived social support and lifestyle factors contribute to the HRQOL experienced in MO

1.5 Comparing health-related quality of life

In order to compare the HRQOL of Gauteng migraineurs and their non-migraine-suffering counterparts, HRQOL data were collected through self-report on the Short Form 6 (SF-6). Diagnosis of MO was made using the revised International Classification of Headache Disorders (Headache Classification Committee of the International Headache Society, 2005b) criteria.¹ The research question addressed was: In what way does the HRQOL of MO sufferers differ from HRQOL of those without MO? Background information suggests that HRQOL of migraine sufferers is poorer than that of healthy cohorts and even sufferers of disorders such as diabetes (Aydemir, Ozkara, et al., 2011; Brown et al., 2008). However, no peer-reviewed data on HRQOL for MO sufferers could be located for South Africa.

¹ The ICHD-III criteria were released in 2013 and were still in beta version at the time that this data were collected. This research was therefore based on the previous criteria, published as the ICHD-II.

1.6 Exploring temperament and pain coping in migraine without aura

The objective was to measure the levels of the four temperament characteristics set out in Cloninger's Psychobiological Theory of Personality (using the Temperament Personality Questionnaire or TPQ) and the pain coping strategy of catastrophizing (on the Pain Catastrophizing Scale or PCS) amongst MO sufferers and NM. Finally, the relationship between Catastrophizing and the temperament categories was explored. Temperament has been indicated as an important aspect in pain coping strategies (Compas, Connor-Smith, & Jaser, 2004; Hachaturova, 2010; Rueda & Rothbart, 2009). The research question addressed was: What is the relationship between the harm avoidance (HA) temperament category and catastrophizing in MO? The work of Mongini and colleagues (Mongini, Fassino, et al., 2005) shows a significant relationship between the HA category of temperament and migraine. In addition, catastrophizing is highly prevalent amongst migraine sufferers as a strategy for coping with pain (Chiros & O'Brien, 2011; Raggi et al., 2012).

1.7 Testing for determinants of health-related quality of life

The objective was to determine the serum concentration of glutamate (on enzyme-linked immunosorbent assay or ELISA) and the relative expression levels of the main neurotransmitter for glutamate (the solute-carrier family 1 glial high affinity glutamate transporter 2, SLC1A2, which is also known as the excitatory amino acid transporter, EAAT-2 on quantitative polymerase chain reaction or qPCR) and the level of perceived social support (on the Social Support Questionnaire, SSQ6). The relationships between HRQOL, neurotransmission of glutamate and the levels of HA, catastrophizing and perceived social support amongst MO subjects were then explored using correlation and regression. The research question addressed was: To what extents do temperament, neurotransmission profile, coping strategy and perceived social support explain the variance in HRQOL in MO? A

number of relationships between these variables are highlighted in the literature. These relationships are discussed in detail in Chapter 4.

1.8 Outline of Chapters

The infographic (Figure 1.1) below outlines the contents of each of the chapters. Reviews of the literature on migraine and HRQOL are found in Chapters 2 and 4, while Chapter 3 provides an overview of the Biopsychosocial Model that is used to guide the approach to this research. The discussion of the method is realized over two chapters (Chapters 5 and 6). The results of the research are also presented over two chapters (Chapters 7 and 8), while the discussion and conclusion of the thesis are found in Chapter 9.

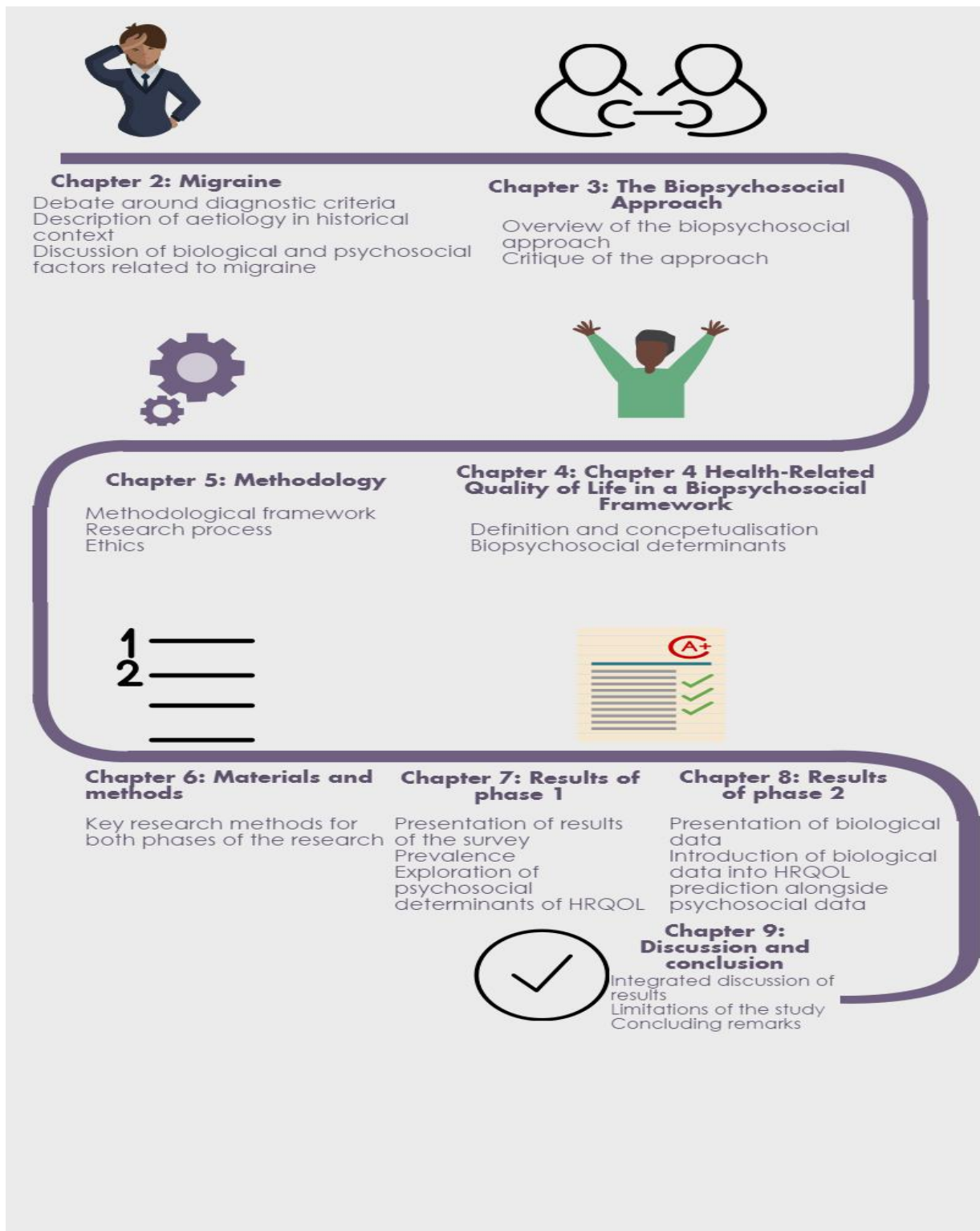


Figure 1-1: Infographic showing the outline of the chapters in this thesis

1.9 Conclusion of Chapter 1

As a chronic pain disorder, migraine has a profoundly negative impact on the HRQOL of sufferers and for many migraineurs this HRQOL does not improve significantly even when the headache abates. In examining the more frequently occurring form of migraine, MO, this thesis aims to provide an improved understanding of which factors may augment or detract from HRQOL in MO. This research will contribute to our understanding of HRQOL in MO. This may further improvements in pain management for all migraine sufferers. The thesis has been approached from a biopsychosocial perspective. Thus potential determinants of MO HRQOL have been examined from the molecular, individual, interpersonal and wider societal levels. The concepts examined in relation to MO HRQOL in the thesis are neurotransmission, temperament, pain coping and perceived social support, with lifestyle factors receiving less emphasis in the literature, but being considered in the analysis.

Chapter 2: Migraine

*I once had a pain in my head,
It started when I was in bed;
But it is my curse it later got worse,
And now I wish I were dead*

(National Headache Foundation, 2006)

An understanding of how migraine without aura (MO) is conceptualised is a necessary step toward hypothesising which factors influence the health-related quality of life (HRQOL) of people suffering from these headaches. The diagnostic classification of the disorder and its historical context are two important focal points in this regard. This chapter therefore begins with a brief account of the efforts to establish diagnostic criteria for migraine, along with a critical discussion of the modern diagnostic criteria, which highlights the tension between evidence-based practice and the dominant diagnostic discourse. The case definition of MO is then provided for this research, based on this discussion.

The chapter then turns to a description of the significant findings on the possible cause of migraine. This discussion on the aetiology of MO is used as an arc into a more detailed discussion of the biological markers and psychosocial indicators of migraine. The chapter concludes with an argument for the integration of biological and psychosocial data in migraine research and the potential benefits thereof.

2.1 The migraine diagnostic criteria

Headaches are regarded as ancient phenomena, and are even referred to in Mesopotamian poems written as early as 3 000 BC (Pearce, 1986; Takano & Nedergaard, 2009; Unger, 2006). The history of migraine begins as an adjunct to this story of general headache. Once the early researchers began to distinguish the distinctive symptoms of nausea,

aura and photophobia, however, the foundation was laid for a separate headache diagnosis, which eventually evolved into the current criteria for migraine. Unfortunately, the diagnosis of migraine has never been a simple practice and consequently, the operationalisation of the criteria in research remains complex (Schürks, Buring, & Kurth, 2009).

2.2 Diagnostic committees.

Though Hippocrates and Celsus (30 AD) are often credited with the discovery of migraine, it was Aretaeus that provided the first comprehensive description of our modern conceptualisation of migraine and referred to it as ‘heterocrania’ (Lane & Davies, 2006; Pearce, 2013). Galen used the term ‘hemicrania’, from which the word ‘migraine’ would finally evolve (Eadie, 2003; Unger, 2006). In 16th century England the term ‘megrim’ was used (following a number of transformations of Galen’s ‘hemicrania’) to describe a form of headache that was associated with nausea and visual disturbance, while in Germany it was called ‘migräne’ and in France ‘migraine’ (Lane & Davies, 2006). Though there was overlap in observations and practices across countries, there does not appear to have been a collaborative effort to define or determine the causes and most effective treatments for migraine till the 20th century.

In fact, it was not until 1962 that an effort was made to create a headache classification system that could be used across nations. The National Institutes of Health (NIH) attempted a headache classification system in that year (McGeeney, 2009). This Ad Hoc Committee on Classification of Headache created 15 headache classes based on the associated pain mechanisms. Though it relied on experimental and clinical data, the committee described the system as “far from complete” (Ad Hoc Committee on Classification of Headache, 1962, p. 179). Migraine was included in the first class of headache, which was referred to as Vascular headache of Migraine Type. The class included five subcategories: Classic migraine, common migraine (now known as MO), cluster headache, hemiplegic and ophthalmologic migraine

and lower-half migraine. A full description of the subcategories can be found in the 1962 publication.

In the 1980s members of the scientific community from various countries collaborated over a three-year period to refine headache classification and diagnostic criteria. This International Headache Society (IHS) consisted of a main committee, 12 subcommittees and interested parties (International Headache Society, 2004). Since then, the classifications of headaches and decisions about their diagnostic criteria have become the domain of the IHS. The committee agreed that the classification criteria for headaches were to be evidence-based as far as possible and that it would prioritise specificity over sensitivity (Headache Classification Committee of the International Headache Society, 2005a).

The IHS publishes updated headache diagnostic criteria as the International Classification of Headache Disorders (ICHD). The first edition of the ICHD was published in 1988 under the title 'Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain'. The second edition appeared in 2004 and the third in 2013 (Boes & Capobianco, 2005; Headache Classification Committee of the International Headache Society, 1988, 2013; Silberstein et al., 2005).

There are three major divisions of the ICHD classification system: (1) Primary headaches, (2) secondary headaches and (3) cranial neuralgias, central and primary facial pain and other headaches. Primary headaches are those that originate in the brain. While secondary headaches are attributed to a disorder that causes headaches - such as neck trauma - primary headaches are not (Headache Classification Committee of the International Headache Society, 2005a). Headaches are organised hierarchically, starting with the major form of the headache and culminating in the sub-forms.

2.2.1 The International Classification of Headache Disorders and migraine.

Migraine is classified as a primary headache and there are six sub-forms of the disorder in the ICHD –II (Headache Classification Subcommittee of the International Headache Society, 2004). Figure 2-1 shows the various subcategories of migraine as described in the ICHD-II. MO is the first sub-form listed.

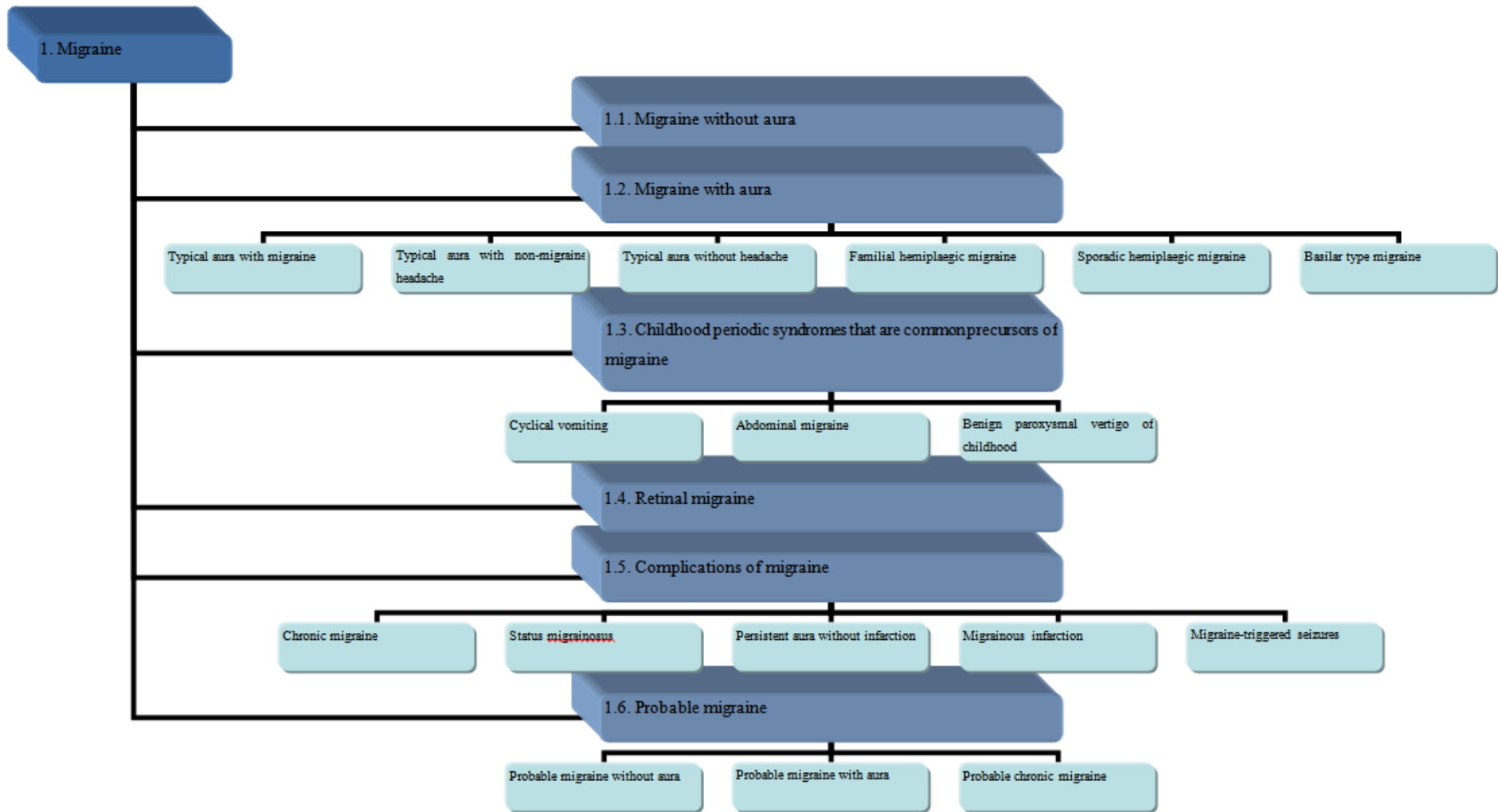


Figure 2-1: Diagnostic subcategories for migraine, according to the International Classification of Headache Disorders – II (Headache Classification Subcommittee of the International Headache Society, 2004)

The focus of this study is on MO, therefore the ICHD criteria for MO are shown in Table 2-1. The criteria for MA have been included for comparison purposes only.

Table 2-1

International Headache Society criteria for migraine with and without aura (Classification Subcommittee of the International Headache Society, 2005)

Migraine without aura		
A. At least 5 attacks fulfilling criteria B-D	B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)	C. Headache has at least two of the following characteristics: unilateral location pulsating quality moderate or severe pain intensity aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)
D. During headache at least one of the following: nausea and/or vomiting photophobia and phonophobia	E. Not attributed to another disorder	
Migraine with aura		
A. At least 2 attacks fulfilling criterion B	B. Migraine aura fulfilling criteria B and C for one of the sub-forms 1.2.1-1.2.6*	C. Not attributed to another disorder
Note: 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.		

**Sub-forms 1.2.1-1.2.6 (also illustrated in Figure 2-1):*

- 1.2.1 Typical aura with migraine headache G43.10
- 1.2.2 Typical aura with non-migraine headache G43.10
- 1.2.3 Typical aura without headache G43.104
- 1.2.4 Familial hemiplegic migraine (FHM) G43.105
- 1.2.5 Sporadic hemiplegic migraine G43.105
- 1.2.6 Basilar-type migraine G43.103

The ICHD-II criteria for probable migraine (previously known as migrainous disorder) simply states that attacks fulfil all but one of criteria A-D (Classification Subcommittee of the International Headache Society, 2005) . This diagnosis allows for the possibility that a participant does not suffer from every single criterion for migraine. Such cases have also been included in this study.

2.2.2 Controversy in diagnosis and the case definition for this study.

The diagnosis of migraine is not without controversy. One disagreement centres on the reliability and validity of the ICHD criteria. Some of the harshest critics of the ICHD call the criteria “arbitrary” (Davies, 2011, p. 34) and feel that they lack biological and clinical validity. For Shevel and Shevel (2014), the controversy is summed up in the statement by the IHS chair, Jes Olesen in a 1994 paper in which he admits that the ICHD criteria were crafted through opinion and were not evidence-based (Shevel & Shevel, 2014).

A further dispute involves the power of the IHS to stipulate how headache is researched. By declaring that no journals should publish studies that do not use ICHD criteria, the IHS has placed the scientific community in a double bind (Shevel & Shevel, 2014) that “undermines advancement in our understanding of headache” (Spierings, 2001, p. 918). Spierings (2001) goes on to propose that the earlier NIH Ad Hoc Committee criteria were in some ways more advanced as the committee that created them left room for modification and admitted shortcomings. Shevel and Shevel (2014) have pointed out that the Headache Subcommittee has removed reference to some of the studies that indicate that decisions have not been taken based on evidence. Reference even to Olesen’s paper has also been removed from the ICHD-III.

Shevel and Shevel (2014) are adamant that there is simply no research data to confirm even the number or duration of attacks chosen as criteria for the ICHD. Furthermore, Shevel

and Shevel point out that the studies that have been used to determine the criteria are inherently biased in their use of the ICHD criteria to determine prevalence. This tautology in diagnostic research is difficult to overcome when conflicting evidence is blocked from peer reviewed publication.

There is also disagreement as to which criteria are compulsory in diagnosis (Schürks et al., 2009). Notwithstanding that ICHD criteria are generally accepted as the gold standard when combined with physician diagnosis, there is acknowledgement that the latter is not possible in large population-based studies and it has therefore become acceptable to use self-reports (Schürks et al., 2009).

A further difficulty – certainly in population-based studies – is the use of laboratory tests to rule out other headache disorders in keeping with criterion E (not attributed to another disorder. This requires that the headaches could not be better accounted for by any of the causes in headache groups 5-12, i.e. it does not appear to be the result of trauma, vascular disease, intracranial pathology, substances, central nervous system infection, disorder of homeostasis such as hypoxia and is not psychiatric, cervicogenic, eye, ear, nose, throat, sinus, mouth or teeth-related). Even for the average patient attending a general practitioner practice and the well-funded researcher, this can become an incredibly time consuming and expensive exercise. Considering the opposition of some researchers and practitioners to the entire ICHD criteria, the value of these laboratory tests has also been questioned (Schürks et al., 2009).

Striking a balance between thoroughness and over-testing is challenging and both can have important outcomes for migraine epidemiology: Too few examinations may raise the question of whether one is really diagnosing migraine when other disorders have not been ruled out with complete histories, physical, neurological and even laboratory examinations (criterion “Not attributed to another disorder” requires that the headaches could not be better accounted for by stipulated conditions). Migraine diagnoses then run the risk of being viewed

as wastepaper basket diagnoses. However, if one runs too many tests, there is the risk of introducing highly irrelevant data and unethically subjecting patients to unwarranted testing.

For the purposes of this research, epidemiological research convention has been followed and the researcher has not relied on laboratory tests to rule out all other headache causes, but has rather made use of self-reporting. The case definition for MO for this thesis includes two types of participants – those that meet the ICHD-II criteria for MO (at least 5 attacks fulfilling criteria B-D of the ICHD-II criteria for MO) and those with probable migraine (attacks fulfilling all but one of criteria A-D of the ICHD-II criteria for MO). In order to satisfy the diagnostic criteria that require other headache forms to be ruled out, participants also could not have a self-reported history of aura or a terminal or degenerative nerve disease.

The possibility of medication overuse headache was not examined and therefore these participants were not excluded from the study. Furthermore, the exact relationship of traumatic brain injury, neck injury, seizure disorders, cancer and infections to the headache could not be established without further specialist investigation. Therefore, the occurrence of these disorders are described in the results but not used as exclusions.

The study exclusions were regarded as a reasonable attempt at ruling out headaches caused by the disorders stipulated in the ICHD-II. However, it is possible that some disorders were not ruled out. For example, glaucoma without nerve damage could not be excluded without ophthalmological examination. It was also assumed that participants under the influence of at least some (high levels of) substances would have excluded themselves from the study as they would not likely have been able to sustain attention for the prolonged period required to complete the extensive questionnaire.

This case definition reflects some of the complexity of the current debates around migraine diagnosis. For further insight into the disorder, attention now turns to the debates on its causes.

2.3 Theories of causality

One element that adds to the complication around migraine diagnosis is the continued enigma of migraine's aetiology. While some forms of MA are clearly genetic in origin, MO's aetiology has proven particularly tricky to uncover (Longoni & Ferrarese, 2006). Although the study of migraine from biological, social and psychological perspectives has led to a better understanding of the impact of the disease, there is still no single unifying explanation for its aetiology (Coppola, Pierelli, & Schoenen, 2009; Davies, 2011; Deshmukh, 2006). What follows is an account of the most significant theories on the aetiology of migraine to date, with the information organised chronologically.

2.3.1 Early theories.

Some of the early common treatments of migraine and other headache symptoms included trepanation and binding of idols (perhaps because pressure on the site was noted to bring pain relief) (Koehler & Boes, 2010; Unger, 2006). More invasive treatment techniques included cauterisation and the insertion of garlic into an incision (Koehler & Boes, 2010).

Binding and trepanation persisted as popular treatments for migraine into the Hippocratic period, when techniques expanded to reflect the dominant medical discourse of the time: The likes of Hippocrates, Galen and Aretaeus held firmly to the belief that a derangement of humors was responsible for the headaches. Consequently, patients were treated using various bloodletting techniques or through the withdrawal of other body fluids using cupping or blistering (Koehler & Boes, 2010; Pearce, 1986, 2013). Galen attributed migraine to an excess of bile (choler), which irritated one side of the brain (Eadie, 2003; Unger, 2006). Pills were therefore administered to aid liver functions (Unger, 2006).

Migraine cases continued to feature in the works of various Byzantine-era physicians such as Oribasius (320–400 AD), Aetius Amidenus (520–575 AD) and Aeginata (625-690) (Androustos, Dimos-Dimitrios Mitsikostas et al., 2009). Meanwhile, religious theories for the

cause of migraine generally portrayed them as a punishment that could be concluded through the performance of good deeds (Unger, 2006). This era also saw the introduction of the use of magnets, lifestyle interventions such as diet and exercise, as well as the early use of electrical treatments (Koehler & Boes, 2010).

In the 7th century Paulus Aeginata (7th century) of Greece described several triggers of migraine, namely noise, light, smells and drinking alcohol (Pearce, 1986). Ibn Sina or Avicenna (973–1037) also acknowledged that particular smells triggered headaches and proposed the use of African ginger as a treatment (Abokrysha, 2009). According to Abokrysha (2009), Avicenna was also the first to propose a neurovascular theory of migraine pathophysiology. However, it is worth noting that Galen had already proposed that arterial pulsation was the cause of the throbbing pain of the headache (Eadie, 2003; Unger, 2006). Caelius Aurelianus (400 AD) of Algeria used the term ‘crotophon’ to denote this throbbing or pounding pain of a migraine, which, according to Aurelianus, co-occurred with vertigo, burning eyes, nausea or emesis (Pearce, 1986).

2.3.2 Neurovascular and neurogenic theories.

In light of Avicenna’s neurovascular theory of migraine, physicians such as Maimonides (1135–1204 AD) proposed that bloodletting be applied to the pulsating arteries that were thought to be the cause of the headaches (Koehler & Boes, 2010). In the Medieval period, European researchers also married mystical and clinical beliefs to explain migraine (Elliot, 1932) through a combination of the hypotheses of Islamic and Christian medical writers (Eadie, 2012). For centuries, mystical beliefs persisted alongside Galen’s theories, and it was not till the 1700’s that this began to change.

Sympathetic nervous system origins.

In 1778, Tissot published his conclusions on the origins of migraine in *Traité des nerfs et de leur maladies* following 20 years of research (Eadie, 2003). It was in the same year that

John Fothergill published his less extensive observations on the subject (Eadie, 2003; Pearce, 1986), though Fothergill designated it “sick head-ach” (Eadie, 2003, p. 414). Tissot attributed the origin of migraine to a disturbance of the stomach of dietary or emotional cause (Eadie, 2003). This theory placed migraine in the category of a sympathetic disorder, stipulating that this headache arose from the stimulation of the sympathetic system via the gut (Eadie, 2003; Latham, 1872).

Nearly a century later, in 1873, Liveing espoused a further neurogenic theory of migraine (Latham, 1872; Liveing, 1872). Liveing’s position was that migraine was caused by a nerve storm and, though he did not reject the hypotheses that the sympathetic nervous system and neurovasculature played roles in migraine, he was unconvinced of their centrality in the headache’s aetiology (Liveing, 1872; Pearce, 1986). On the other hand, Latham drew the conclusion that it was sympathetic hyperactivity that led to decreased cerebral blood flow, which caused aura, followed by sympathetic exhaustion and vasodilation that caused the headache (Eadie, 2005; Latham, 1872).

Latham’s conjecture that aura and headache pain are caused by two distinct, yet related processes, is an important one. At present there is evidence that, while vascular changes in migraine are related to the mechanism behind aura, they are in fact not the primary cause of headache pain (Davies, 2011). This area of research was significantly advanced by the works of Leão and Wolff, which are described later in this chapter.

Around the late 19th century, Woakes proposed the use of ergotamine in migraine treatment (Koehler & Isler, 2002). Woakes and at least three other prominent researchers of the time, Romberg, Symonds and Anderson, attributed migraine to neuralgia of the trigeminal nerve branches (Eadie, 2005). However, the proposed involvement of the trigeminal nerve in migraine pathogenesis was usurped by sympathetically-related hypotheses: du Bois-Reymond surmised that hyperactivity of the cervical sympathetic system caused cranial vasoconstriction (Pearce, 1986); Moller suspected sympathetic paralysis resulting in vasodilation (Eadie,

2005). These two divergent views were consolidated by Wilks and Moebius in the 1890's, with Wilks reworking the gastric hypothesis to suggest that this dysfunction resulted in paresis of the brain blood vessels (Eadie, 2005). Unfortunately, Wilks did not provide clear descriptions of the mechanism connecting the gut and the brain, but Eadie (Eadie, 2005) posited that Wilks would have connected the two via the autonomic nervous system. On the other hand, Moebius's conjecture was that some initial alteration in brain functioning caused increased cervical sympathetic tone, which led to a change in cranial blood flow (Eadie, 2005; Latham, 1872). In 1900 Deyl specified compression of the trigeminal nerve as the root of migraine pain (Unger, 2006), thus adding to the neurological theories of the headache.

Wolff's contribution.

The 20th century saw the emergence of more detailed explanations of how pathological neurological processes lead to neurovascular abnormalities in migraine. One of the most important discoveries was that of Wolff and Graham, who, in 1938, demonstrated the efficacy of ergotamine in constricting blood vessels and effectively ending a migraine (Baron & Tepper, 2010; Unger, 2006). Wolff's work was vital in showing that the pain emanated not from the insensate neurons but from the highly sensitive neurovasculature (Unger, 2006) by demonstrating that stimulation of the blood vessels of the meninges and the cerebrum resulted in severe headaches, but stimulating the brain parenchyma did not (Parsons & Strijbos, 2003). Subsequently, Wolff's work ascribed aura to intracranial spasm of the cerebral arteries and headache pain to extracranial vasodilation leading to activation of nociceptors (Shevel, 2011). Shevel (2011) points out that, while Wolff's surmise about the origins of aura was disproved by Oelsen's Copenhagen Group, the theory that extracranial vasodilation causes headache pain has not been discredited. It was in 1948 when Wolff's first edition of *Headache and Other Head Pain* was published (Weatherall, 2012). The text is now in its eighth edition and is regarded as the definitive text in the field (Geweke, 2006).

Cortical spreading depression and oligoemia.

The history of migraine in the Middle ages is replete with the accounts of Hildegard of Bingen, a nun that described her experience of aura in great detail (Alexander, 2014).

Hildegard's symptoms have been diagnosed retrospectively as MA and her depictions of her symptoms have provided insight into the subjective experience of aura and headache pain (Foxhall, 2014).

Our current understanding of the mechanism behind aura is attributed to the works of Leão, who documented cortical spreading depression (CSD) in the 1940's. In 1941 Lashley analysed his own visual auras and hypothesised that they were caused by excitation of the visual cortex, followed by reduced neuronal excitability (Wolthausen, Sternberg, Gerloff, & May, 2009). A few years later, Leão sought a clearer understanding of the electro-encephalogram results seen in experimental epilepsy through his experiments on rabbits, (Leão, 1944). One of his findings was that tetanizing current caused an enduring period of depressed spontaneous electrical brain activity. In migraine, CSD describes the slow propagating wave of neuronal burst activity, which is followed by depression of activity - both spontaneous and evoked (Charles & Brennan, 2009; James, Smith, Boniface, Huang, & Leslie, 2001; Schwedt & Dodick, 2009).

Leão's rabbits showed how the depression spread slowly from the point of origin all across the cortex and led to inhibited somatosensory and optic responses (Leão, 1944). The researcher posited a similarity between CSD and epileptic activity – phenomena he described in rabbits, cats and pigeons (Charles & Brennan, 2009). It was only in the 1950's that the similarity was noted between CSD and migraine (Milner, 1958).

Leao (1944) also posited that CSD neuronal activity predicts changes in cerebral blood flow. Specifically, he suspected that a vasodilator was released, resulting in a pattern of marked vasodilation co-occurring in the region of the depression. This vasodilation of the meningeal and cortical blood vessels has been described as a powerful endogenous activator

of meningeal nociceptors via inflammatory pathways (Theoharides, Donelan, Kandere-grzybowska, & Konstantinidou, 2005). Thus, migraine pain (the headache) was deduced to be vascular in origin. However, this conclusion has been weakened somewhat by neuroimaging findings, which suggest that hyperaemia in aura is followed by oligoemia, which continues into the pain phase, therefore indicating that vasodilation cannot account for the pain (Davies, 2011). When CSD occurs, regional cerebral blood flow (rCBF) actually increases only during the depolarisation phase and then decreases once neuronal activity diminishes (Wolthausen et al., 2009). Thus, while neuro-imaging has confirmed neurovascular involvement in migraine, it has also indicated that vascular changes are not the primary cause of the migraine pain (Davies, Macfarlane, McBeth, Morriss, & Dickens, 2009).

This conclusion remains controversial in terms of MO, though, as regional cerebral blood flow (rCBF) changes are not consistently related to CSD in MO (Headache Classification Committee of the International Headache Society, 2013). There is, in fact, still uncertainty as to whether CSD is a general feature of all migraine or specific to MA (Headache Classification Committee of the International Headache Society, 2013).

Rather than elaborating on the physiological mechanisms of CSD, the focus is placed on the discussion of how the concept has become an important focal point for the distinction between MO and MA. Descriptions of the mechanism of CSD can be found in Busija, Bari, Domoki, Horiguchi, and Shimizu (2008) and Charles and Brennan (2009).

In a review of recent brain imaging findings, Davies (2011) discusses how findings from SPECT, DTI and PET studies have led to a more in-depth understanding of CSD, the distinction between and, ultimately, the question of how CSD relates to each of the two migraine subtypes. It is generally agreed that CSD is the primary cause of migraine aura (Charles & Brennan, 2009), but not a prerequisite for migraine (Wolthausen et al., 2009). On the other hand, there may even be some form of silent CSD that occurs in deep structures and is not recorded by surface EEG (Davies, 2011; Wolthausen et al., 2009).

While many concur with Schoenen (2006) that imaging has given us more insight into the origins of migraine, research with the technique has also raised a few questions. One of these questions pertains to our assumption that MO and MA are merely variations of the same disorder. This issue was first raised in Chapter 1 in relation to the choice of MO as opposed to migraine in general or MA as the population for this study. In Chapter 1 it was highlighted that MA and MO differ vastly in their characteristics (Christensen, Le, Kirchmann, & Olesen, 2012; Ludvigsson, Hesdorffer, Olafsson, Kjartansson, & Hauser, 2006; Russell, Rasmussen, Fenger, & Olesen, 1996; Russell et al., 2002). As noted by Schoenen (2006):

Striking features of results obtained with neurophysiological investigations in migraine are their heterogeneity and variability. This should not come as a surprise, however, if one keeps in mind that the migrainous diathesis is a functional one, modulated by various internal and external factors and markedly heterogeneous from a genetic point of view. Most likely, the future of neurophysiologic testing in migraine is therefore to contribute to a better phenotyping of subgroups of patients for genetic and therapeutic studies and possibly to the identification of dynamic functional changes that modulate the disorder and may chronicise it. (p. S79)

When taking this observation to its extreme, the continued placement of MA and MO under the same umbrella requires further consideration. A population-based case control study conducted amongst Icelandic children diagnosed with migraine ($n = 94$) showed that children with MA had a 3.7-fold increased risk for developing epilepsy when compared to controls, whereas this risk was not apparent in the children with MO (Ludvigsson et al., 2006). For the authors, this result is suggestive of two different disease processes and therefore two different disorders. This is hardly a new notion, though, and a similar observation was made in a study of 484 adult migraineurs in Denmark (Russell, Rasmussen, Fenger, & Olesen, 1996). In that study, the authors investigated premonitory symptoms, precipitating factors, hormones, symptomatology and demographic variables in MO ($n = 342$) and MA ($n = 156$) sufferers.

Results indicated a distinct clinical presentation for each headache type characterised by clear differences in the age of onset, sensitivity to female hormones and bright light. This, in conjunction with the different neuroimaging results for MA and MO present a convincing argument for the two as separate entities.

Sterile inflammation.

Sterile inflammation refers to the inflammatory response arising in the absence of microorganisms. Though it contributes to the body's efforts to clear debris and promote repair, it may also arise from ischaemia-reperfusion, autoimmunity or the presence of sterile foreign particles. In some cases, this inflammatory response becomes uncontrolled, resulting in inflammation-derived injury and even further inflammation (Menezes, Mansur, McDonald, Kubes, & Teixeira, 2011). Possibly the most detailed description of sterile inflammation comes from Miskowitz's neurovascular theory of migraine (Coelho et al., 2007).

Miskowitz explains that both extrinsic (occurring outside the central nervous system) and intrinsic (within the central nervous system) nerves are stimulated in migraine. This process is depicted in Figure 2.1-1: Extrinsic nerves include the peripheral nerves arising from the superior cervical (SCG), sphenopalatine (SPG), otic (OG) or trigeminal (TG) ganglia. Intrinsic nerves originate in the parenchyma and microvasculature. Large cerebral vessels, pial vessels, large venous sinuses and the dura mater are surrounded by fibres of the TG. These blood vessels are innervated by noradrenergic (NA), serotonergic (5-HT), cholinergic (Ach), glutamate (Glu) or gamma amino butyric acid (GABA) afferents from subcortical neurons of the thalamus, locus coeruleus (LC), raphe nucleus (RN), basal forebrain, or the local cortical interneurons. Stimulation of these afferents causes vasoactivation (Hamel, 2006). Both MA and MO show similar subsequent processes of pro-inflammatory secretion, oxidative stress, leukocyte activation, inflammation and dilation of intracranial and extracranial arteries on the side of the headache. Inflammation is mediated by Substance P (SP), calcitonin gene-related peptide (CGRP), neurokinin A (NKA), neuropeptide Y (NPY),

Somatostatin (SOM) and endothelin-3. This repeated process can cause damage to the blood vessels. Tachykinins change vascular permeability and CGRP causes vasodilation in what is known as the axon reflex flare. This vasodilation activates intracranial nociceptors (Hamel, 2006), leading to the pain experienced in the headache.

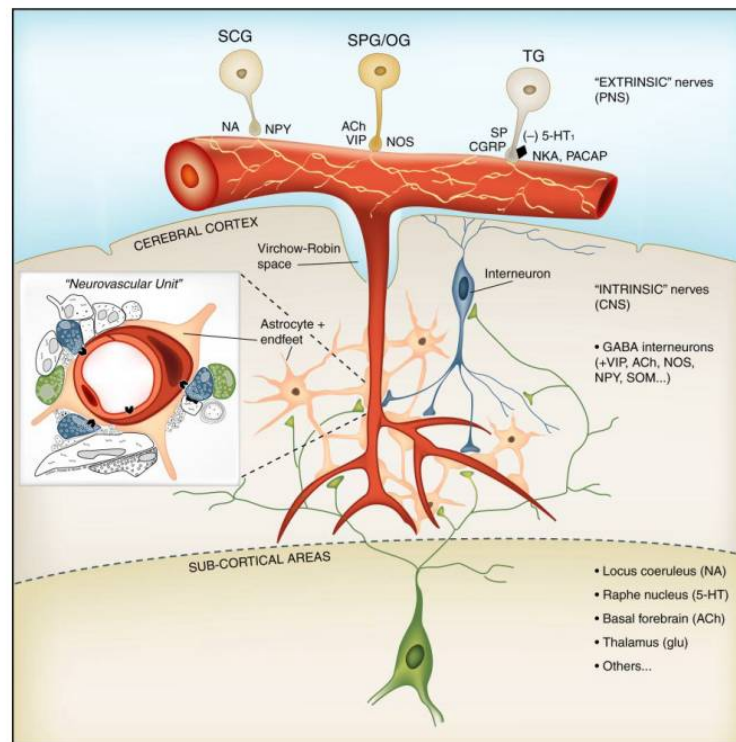


Figure 2-2. Regulation of vascular tone via the intracranial perivascular nerve (Hamel, 2006, p. 1060)

Central and peripheral sensitisation.

The modulation of pain is a complex process with numerous potential sites for disruption and dysfunctional pain experience. Both central and peripheral sites have been identified as being involved in causing migraine pain (Aguggia, 2012) through processes of allodynia and hyperalgaesia.

Allodynia is the evolution of a pain response in the presence of a non-noxious stimulus (Granziera et al., 2014). Hyperalgaesia is seen when stimuli that previously produced minimal pain responses begin to cause increased pain (Chapman, Tuckett, & Song, 2008;

Sarchielli, Di Filippo, Nardi, & Calabresi, 2007). Both allodynia and hyperalgesia are features of migraine that result from abnormal cortical excitability (Granziera et al., 2014). According to Granziera et al. (2014), thalamic neurons receiving afferents from the cranial meninges and extracephalic skin are sensitized in migraineurs, resulting in the reported whole body allodynia and hyperalgesia. In addition, the posterior thalamus integrates nociceptive signals from the dura mater and retinal photosensitivity, providing a possible reason for the increase in pain perception in bright light (Granziera et al., 2014).

The observation that migraine often becomes a chronic and even daily occurrence for many sufferers (Galletti et al., 2009) has led to investigation of possible enhanced nociception in such patients. Reduced functioning of pain control pathways, which compounds the pain arising from the inflammatory process has been posited (Goadsby, Ferrari, Csanyi, Olesen, & Mills, 2009; Hamed, 2009; Hamel, 2006).

The concept of cortical hyperexcitability in migraine relates to a lack of habituation to evoked stimuli over various modalities, although it is not clear if this deficient habituation is caused by increased sensitivity or decreased inhibition. A neuron is considered to be hyperexcitable when it responds to subliminal stimulus or produces response of increased amplitude to supraliminal stimulus (Coppola et al., 2009). What is clear is that migraine sufferers have a low threshold for the attack and often do not recover from this inter-ictally. This suspected subclinical central impairment has given rise to the term “the migrainous brain”. Alteration of mitochondrial energy metabolism, ion transporter dysfunction and altered neurotransmitter levels have been considered possible causes of the low threshold (Coppola et al., 2009).

2.4 Determinants of migraine

While the exact cause of migraine still eludes us, researchers have, nevertheless, managed to amass a significant body of work on correlates of migraine. The following sections deal with the proposed biological and psychosocial markers of migraine in general and MO in particular.

2.4.1 Identified biomarkers.

No single biological substrate has yet proven viable and feasible as an accurate means of diagnosing migraine. Without a biomarker for migraine diagnosis, practitioners have to rely on subjective criteria (Colson, Lea, Quinlan, MacMillan, & Griffiths, 2005), which can be unreliable and lead to protracted diagnosis processes. The neurological alterations in migraine are both centrally and autonomically located and separating MA and MO or even describing an overall pathophysiology for all migraine types has been complicated.

Markers are mainly tested through samples from blood and CSF, but electrophysiology and neuro-imaging techniques are also widely used. Proposed biomarkers for MO include genes related to catecholamine metabolism (COMT), lipoprotein transport (LDL-R) and Human Leukocyte Antigen (HLA-DRB1) (Loder, Harrington, Cutrer, Sandor, & De Vries, 2006; Montagna, 2008; Nagata et al., 2009).

2.4.2 Genetic determinants of migraine without aura.

To date, no fewer than ten genes have been studied in relation to migraine. The clearest genetic outcomes are seen in studies of familial hemiplegic migraine (FHM). The conclusion is that FHM has a Mendelian pattern of autosomal dominant heritability (Nagata et al., 2009). The following genes have previously been studied in FHM patients: genes associated with channelopathies (P/Q neural calcium channel, Na⁺/K⁺ ATPase and voltage-gated sodium channel); neurotransmitter genes (5-HTSERT, 5-HT2A, dopamine receptor 2 or DRD2 and dopamine betahydroxylase) and genes that code for a host of other proteins

including low density lipoprotein (LDL) and LDL receptors, Factor V R/Q 506, protein S, angiotensin converting enzyme, methylene-tetra-hydrofolate reductase, progesterone receptors, K⁺ channel KCNN3 and human leukocyte antigen (HLA-DRB1) (Montagna, 2008; Nagata, Hattori, et al., 2009; Norton et al., 1999; Schurks et al., 2009; Stewart, Simon, Shechter, & Lipton, 1995; Striessnig, 2005). However, the genetic study of the more common non-familial migraine has yielded less conclusive outcomes, leaving a great scope for further research (Montagna, 2008).

The genetic study of the more commonly occurring non-familial type of migraine – including MO - has yielded less conclusive outcomes (Rainero et al., 2006). There is evidence that first-degree relatives of MO probands have 1.9 times the risk of developing MO and 1.4 times the risk of developing MA, whereas first-degree relatives of MA probands have nearly four times the risk of developing MA and no increased risk of developing MO (Montagna, 2008). Meanwhile, some studies show moderate effect sizes in voltage-gated channel gene-MO interactions (Nyholt et al., 2008). Recently, a body of evidence has begun to grow around the involvement of glutamate in migraine.

2.4.3 Glutamate in migraine.

Given the prominent role of glutamate transport in pain hypersensitivity (Mathew, 2001; Sarchielli, Di Filippo, Nardi, & Calabresi, 2007) it is not surprising that glutamate has been tied to migraine. Both pre-clinical and clinical observations have led to a fairly clear indication of glutamate involvement in migraine, although researchers have not been able to pinpoint its exact role (Ramadan, 2003; Vikelis, 2007).

The argument for glutamate involvement in migraine is evinced by studies showing that glutamate antagonists have had some success in migraine treatment (Andreou & Goadsby, 2011; Lampl, Buzath, Klinger, & Neumann, 1999). Additionally, elevated glutamate levels have been noted in both MA and MO (Alam, Coombes, Waring, Williams, &

Steventon, 1998; Cananzi, D'Andrea, Perini, Zamberlan, 1995), with a fair indication that glutamate levels are higher in MA than MO inter-ictally, with levels climbing higher during attacks (Ferrari, Odink, Bos, Malessy, & Bruyn, 1990). While glutamate is implicated in CSD (Eikermann-Haerter, Kudo, & Moskowitz, 2007), it is also a known stimulant of the trigeminal nucleus caudalis (illustrated in cats by Storer and Goadsby cited in Chasman et al., 2011), which ties the neurotransmitter to central sensitization. The evidence suggests that, while the neurotransmitter may be involved in both types of headache, it may play varying roles in the pain.

The elevated levels of glutamate in migraine have been further investigated at the cellular level and linked to impaired uptake into platelets (Cananzi, D'Andrea, Perini, Zamberlan, et al., 1995; Vaccaro et al., 2007). Vaccaro et al. (2007) explored platelet glutamate uptake and release in 25 MO, 25 MA and 20 health controls. While MO subjects showed increased glutamate release from platelets into plasma, they also exhibited decreased platelet uptake relative to controls. There was also an increased plasma glutamate level in MO relative to controls. The authors refer to the role of SLC1A2 in this process, suggesting that transport of glutamate is altered in MO. The hypothesis is thus that defective cellular glutamate uptake is an aetiological mechanism in MO.

There are, however, some research results that indicate that glutamate really plays a definitive role in chronification of MO (Sarchielli, Di Filippo, et al., 2007; Vargas, 2009). The discovery of the -181 A/C polymorphism of the SLC1A2 transporter promoter region has provided evidence of defective glutamate transport in chronic forms of migraine. The observation was made by Shin and colleagues (Shin, Han, Lee, & Park, 2011) that the A allele of this polymorphism is related to higher analgesic use (and therefore possibly transformation to medication over-use headache) amongst migraineurs is considered a vital clue to the potential mediating factors in migraine pain. The importance of examining temperament in migraine is also highlighted by Shin et al.'s research in which it is shown that the occurrence

of the A allele (A/A and A/C) is associated with lower Reward Dependence (RD) scores than in C/C groups. This relationship is apparent in females, but not males (Matsumoto et al., 2007).

Genome-wide association studies (GWAS) have given rise to a more complex picture of glutamate's role in migraine. In the discovery stage of Anttila et al.'s GWAS using seven European case collections (Anttila et al., 2010), 429 912 markers were successfully genotyped using Online Methods. When Cochran-Mantel-Haenszel (CMH) association analysis ($P < 5 \times 10^{-8}$) was conducted, only one significant marker was identified - the minor allele (A) of rs1835740 on chromosome 8q22.1 [$p = 5.38 \times 10^{-9}$; $OR = 1.21$ to 1.33 (95% CI 1.115 – 1.528)]. Although replication was only successful in the larger groups, a stronger effect was noted amongst those with MA. Rs1835740 was found to lie between two candidate genes, metadherin (MTDH) and plasma glutamate carboxypeptidase (PGCP). The expression of quantitative trait locus (eQTL) conducted using fibroblasts, T cells and lymphoblast cell lines showed significant correlation with transcription levels of MTDH in the lymphoblasts. Rs1835740 is a cis regulator of MTDH expression in lymphoblasts. In astrocytes MTDH down-regulates SLC1A2 (aka EAAT-2 or GLT-1) and knock-out mice lacking SLC1A2 suffer lethal spontaneous epileptic seizures. PGCP on the other hand is responsible for the hydrolysis of various substrates to form glutamate. The authors propose that down-regulation of SLC1A2 (the main glutamate transporter in the brain) or increase in PGCP activity causes an accumulation of glutamate in the synaptic cleft, which leads to the central sensitization and the CSD seen in migraine. They add that SLC1A2 transporter functional alteration is also linked to ataxia and epilepsy, two other episodic neurological disorders.

On the other hand, Ligthart and colleagues (Ligthart et al., 2011) found less convincing results with respect to MTDH. They conducted a meta-analysis of GWAS in six European migraine cohorts obtained from Dutch and Icelandic databases. In total, the sample in the exploratory phase consisted of 2446 migraine cases and 8534 controls. The SNP,

rs9908234 emerged as a candidate for migraine ($p= 8 \times 10^{-8}$). This SNP is located in the Nerve Growth Factor (NGF) receptor gene. In silico methods did not replicate these results in any of the three additional cohorts from the Netherlands and Australia. Comparison of the findings with other studies' migraine gene and loci findings were not significant. In addition, only a modest association with MTDH was found.

Some GWAS have focused specifically on MO. Christensen, Le, Kirchmann, and Olesen (2012) followed the GWAS by Anttila et al. (2010) with an investigation of the rs1835740 relationship to MO. They could find no statistically significant relationship between that allele and symptoms, comorbidity, provoking factors or the effect and use of different medical treatment in MO. A later GWAS by Freilinger, Anttila, Vries, and Malik (2013) identified six loci with genome-wide significance. Six SNP's were identified on 1q22, all of which are located within the gene for the myocyte enhancer factor 2D (MEF2D). MEF2D supports newly formed neurons, but also regulates the formation of excitatory synapses. Aside from identifying four new associations with MO, Freilinger et al.'s (2013) study also confirmed the conclusions of an earlier study that implicated TRPM8 and LRP1 (Chasman et al., 2011).

Brief overview of glutamate in the human central nervous system.

In-depth investigation of the biochemistry and neurophysiology related to glutamate is beyond the scope of this thesis, but some background is required to understand glutamate's significance in MO. A brief overview of glutamate's role in normal human central nervous system functioning and psychopathology is given. The reader is referred to more detailed accounts of some topics throughout the section.

Glutamate is an anion of the amino acid, glutamic acid (Amiel & Mathew, 2007). As the main excitatory neurotransmitter in the human central nervous system glutamate has vital roles in higher cognitive functions, memory, learning and development (Cater, Vandenberg, & Ryan, 2014). Glutamate is distributed widely throughout the brain as it is required in

protein synthesis, intermediate metabolism, as a precursor for the human body's main inhibitory neurotransmitter, γ -amino butyric acid (GABA) and in ammonia detoxification (Behar & Rothman, 2001; Broman, Hassel, Rinvik, & Ottersen, 2000).

Glutamate is found in various foods, but is also produced in the human body from glutamine in the presence of glutaminase and from α -ketoglutarate via alanine aminotransferase (Behar & Rothman, 2001; Whillier, Garcia, Chapman, Kuchel, & Raftos, 2011). The dominant pathway for brain glutamate metabolism is the glutamine-glutamate cycle (also referred to as the glutamate/GABA-glutamine cycle) that occurs between astrocytes and neurons (Behar & Rothman, 2001).

Depolarization of the presynaptic neuron leads to the release of glutamate into the presynaptic cleft, where glutamate binds to receptors on the postsynaptic glutamatergic neuron, leading to the opening of the ion channels in the post-synaptic membrane (Behar & Rothman, 2001; Cull-Candy, 2002). Glutamate receptors are expressed in various permutations giving rise to a variety of glutamate effects (Cull-Candy, 2002). There are several ionotropic glutamate receptors, the most important of which are kainate, α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and N-methyl-D-aspartate (NMDA) as well as three metabotropic receptors (mGluR). Full reviews of these receptors can be found in Cull-Candy (2002) and Ferraguti and Shigemoto (2006).

The reuptake of glutamate from the synaptic cleft into astrocytes is accomplished through transporters. There are five high-affinity glutamate transporters that have been cloned in humans (named excitatory amino acid transporters or EAAT 1 to 5). SLC1A2 is the major transporter of glutamate in the human, being responsible for up to 90% of glutamate transport (Rainesalo, Keränen, Saransaari, & Honkaniemi, 2005; Shin et al., 2011). Transport is Na^+ -dependent and requires the co-transport of Na^+ and H^+ and counter-transport of K^+ (Behar & Rothman, 2001).

Once in the astrocyte, glutamate is converted to glutamine through the uptake of an ammonia group in the presence of glutamine synthetase. This glycine is used by the presynaptic neuron to produce glutamate (mediated by phosphate-activated glutaminase). This is a rather simplistic representation of the fate of glutamate in the astrocyte, but it will suffice for this thesis. For more detailed accounts the reader is referred to Bak, Schousboe, and Waagepetersen (2006); Behar and Rothman (2001); Hertz (2013) and Petroff, Errante, Rothman, Kim, and Spencer (2002).

Glutamate and pathology.

Excess glutamate causes cytotoxicity and its concentration therefore needs to be carefully regulated. In healthy humans the serum levels of glutamate vary between 10 and 100nmol/ml (Heresco-Levy et al., 2007). In toxic events (extracellular glutamate higher than 100micromol/l, glutamate is oxidised in addition to undergoing conversion in the glutamate-glutamine cycle (Behar & Rothman, 2001).

Increased levels of glutamate have been documented in hypoxia and hypoglycaemia (Danbolt, 2001), stroke (Aliprandi et al., 2005; Mallolas et al., 2006) and epilepsy (Chapman, 2000; Meldrum, 2000; Petroff et al., 2002). Furthermore, heightened glutamate levels have been associated with the C allele of the -181 A/C polymorphism of the SLC1A2 transporter promoter region in the poorer outcomes of at least two neurological disease states, namely stroke and multiple sclerosis (Mallolas et al., 2006; Pampliega, Domercq, Villoslada, & Sepulcre, 2008). Glutamate regulation is also an important aspect of pain hypersensitivity (Mathew, 2001; Sarchielli, et al., 2007) and glutamate receptors are now targets for drug treatments in chronic pain conditions (Bleakman, Alt, & Nisenbaum, 2006).

The potential role of glutamate transporter disturbances in mood disorders has led to possible novel therapeutic agents (Hashimoto, Sawa, & Iyo, 2007; Krystal et al., 2002). Meanwhile, glutamatergic systems are also being scrutinised for their role in drug resistance in the treatment of schizophrenia (Hong, Yu, Lin, Cheng, & Tsai, 2001).

2.4.4 Psychosocial markers in migraine.

The variable results even in GWAS suggest that genetic changes are not the only determinants of the occurrence of migraine. The emergence of epigenetic principles leads to questions regarding possible chromatin modifications in migraine. The pain experienced during MO attacks is variable (Diego, Vuillaume De Diego, & Lanteri-Minet, 2004) and has a significant impact on the patient, with some patients unable to sleep, eat or complete daily activities (de Velasco & Gonzalez, 2003). While the occurrence of migraine pain has been explained in some measure by sensitisation of meningeal nociceptors and sterile inflammation (Longoni & Ferrarese, 2006), there is support for the involvement of psychosocial factors in the experience (Blomkvist, Hannerz, Katz, & Theorell, 2001; Fasmer, Akiskal, Kelsoe, & Oedegaard, 2009; Tietjen et al., 2010a, 2010b, 2010c; Tietjen & Peterlin, 2011).

Temperament.

Work on the processing of pain-related words has shown that there is enhanced sensitivity of the pain neural matrix in migraine patients over healthy subjects (Eck, Richter, Straube, Miltner, & Weiss, 2011). Moreover, personalities characterised by high emotionality are likely to experience high emotional burden related to their experience of pain (Mongini et al., 2009). The latter implies a relationship between the basis for personality (temperament) and pain regulation. For the purposes of this research, temperament is conceptualised using Cloninger's Psychobiological Model of Personality, which takes into account state, trait and environmental aspects of personality. Cloninger's theory describes four independent dimensions of temperament, namely Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P). NS is related to the level of activation of exploratory activity, while HA indicates the efficiency of the behavioural inhibition system. RD is related to the maintenance of rewarded behaviour, whereas P indicates maintenance of behaviour as resistance to frustration (Hansenne et al., 1999).

These temperament traits are underpinned by different neurobiological systems: NS is related to the functioning of the dopaminergic system and high NS is characterized by low basal DA, whereas HA is regulated by the serotonergic system and high HA is related to high serotonin activity. RD appears to be related to the noradrenergic system and low basal NA. Meanwhile, P is regulated by the glutamate system (Conrad et al., 2007; Hansenne et al., 1999; Mongini, Keller, Deregibus, Barbalonga, & Mongini, 2005). These assumptions underlie the core of this research question, which is whether the pain experienced in migraine is associated with temperament traits and regulated by neurotransmission.

It was Wolf who, in 1937, termed the observed dominant personality traits and reactions in migraine sufferers “migraine personality”. However, research has not been conclusive in its definition of this psychological profile and Wolf’s description of resentment and neuroticism amongst migraine sufferers has been refuted in some instances. Likewise, findings around temperament in migraine have been variable (Abbate-Daga et al., 2007). Nylander et al. (1996), Di Piero et al. (2001) and Boz et al. (2004) could find no significant temperament trait differences between migraineurs and controls. By contrast, Mongini (2005) found that migraine sufferers ($n = 49$) scored significantly higher than the controls in HA ($p = .021$) and P ($p < .001$). The significantly elevated HA scores have been confirmed in a later study of 142 migraine patients, 108 healthy controls and 30 patients with non-migrainous chronic pain (Sánchez-Román et al., 2007). These findings indicate a possible temperament component in migraine.

Parent-child relationships.

A few studies conducted in the past decade have shed light on interesting dynamics that exist between parents of migraineurs and their children. For example, Esposito et al. (2013) studied 219 children referred for MO and 381 healthy controls. The Italian version of the Separation Anxiety Test was administered and daily headache diaries were kept to record information on headache frequency and duration. Whereas insecure/avoidant attachment

(Type A) was positively related with the intensity ($r = .375, p < .001$), frequency ($r = .392, p < .001$) and duration ($r = .184, p = .006$) of MO attacks, insecure/ambivalent attachment (Type C) was negatively related with the frequency ($r = -.348, p < 0.001$) and intensity ($r = -.305, p < .001$) of the attacks. Secure attachment (Type B) was negatively related with the duration ($r = -.229, p < .001$) of the attack. These results indicate that avoidant attachment is a risk factor for more frequent and painful MO headaches, albeit that the relationship is not very strong.

The article by Esposito, Roccella, Gallai, et al. (2013) explored the relationship between maternal personality (on the Minnesota Multiphasic Personality Inventory (MMPI-2)) and frequency, intensity, and duration of migraine attacks in their children who suffer from MO ($n = 422$) and healthy children ($n = 587$). Results indicate that the mothers of the children with MO have a number of significantly higher indications of psychopathology (e.g. paranoia, social introversion and anxiety and low self-esteem) than the mothers of the healthy children ($p < .05$). The frequency with which MO attacks occurred in the children was significantly correlated with the mothers' anxiety ($r = .4903, p = .024$) and maternal low self-esteem ($r = .5130; p = .017$), while the duration of the attacks was significantly correlated with a number of the mothers' psychological problems - especially hypochondriasis ($r = .6155, p = 0.003$), hysteria ($r = .6235, p = .003$) and health concerns ($r = .7039, p = .001$). The authors concluded that the mothers' personalities affect the children's experiences of their attacks. They posit that parental modelling is central to teaching children to cope with their own health problems and that this can have a significant impact on how often, how long and how intensely symptoms recur.

Adverse early life events.

Several studies indicate that traumatic life experiences are highly prevalent amongst those suffering from migraine. For example, Tietjen et al. (2010) reported 21% physical abuse, 25% sexual abuse, 38% emotional abuse, 22% physical neglect and 38% emotional

neglect amongst migraineurs ($N = 1348$). A prevalence study conducted amongst 13089 Canadians showed that people with a history of childhood physical abuse were twice as likely to have a migraine diagnosis as those that had not been abused $OR = 2.27$ 99% $CI [1.80, 2.86]$ (Fuller-Thomson, Baker, & Brennenstuhl, 2010). The relationship between migraine and childhood physical abuse was significant even when controlling for a number of confounders.

These traumatic events moderate the relationship between migraine and headache disability and even chronicity. Epigenetics provides a clue to understanding the impact of these events (Rothrock, 2010).

Stress.

The physiology of stress is well documented and the details are not the focus of this study. The reader is therefore directed to the numerous resources dealing with the neurobiology of stress for further information (e.g. McEwen, Elland, Hunter, & Miller, 2012; McEwen, 2012; Tsigos & Chrousos, 2002).

Borsook and colleagues (Borsook, Maleki, Becerra, & McEwen, 2012) reflect on this relationship between stress and migraine and conceptualise the effects of migraine on the brain in terms of allostatic load. Migraine sufferers report a high level of negative stressors and traumatic life events (Autret, Roux, Rimbaux-Lepage, Valade, & Debiais, 2010; Branch, 2009; Tietjen et al., 2010b, 2010c) and the headache itself can serve as a stressor. When the attempts to maintain physiological stability (allostatic responses) become maladaptive, the stress response becomes dysfunctional. Such alteration to the stress response can alter brain structure and function through plasticity, which further augments the dysregulation. In migraine, this means that psychosocial stressors and the neurobiological response to these (and to the headache) all contribute to the subjective experience of the headache – and, by extension, a poor HRQOL.

Stress is of particular importance in migraine for Martin (2007): In earlier work, Martin and Soon (1993) showed that perceived stress amongst migraine sufferers was higher

than amongst controls, while migraineurs were also much less satisfied with their social support than controls. Martin and Soon conclude this to mean that the psychosocial elements of migraine require further investigation.

Sauro and Becker (2009) added to Martin and Soon's (1993) surmise about the role of stress in migraine by explaining that migraine onset appears to follow a stressful period (sometimes called the let-down period). This is known as the Stress-Relaxation Model (Robbins, Lipton, Laureta, & Grosberg, 2009). Lipton and his colleagues (Lipton et al., 2014) provided evidence to support this Stress-Relaxation Model in 17 migraineurs. Hashizume et al. (2008), on the other hand, examined the perception of daily hassles in 16 migraine patients. The results indicate that sufferers perceive a higher burden of daily hassles in the 1-3 days leading up to their migraine versus other days.

Coping.

The association between mood (depressed mood and irritability), cognitive symptoms (memory and attention deficits) and migraine was originally reported by Living in 1895 (Pompili et al., 2010). Recent evidence correlates migraine with substance use and a number of psychiatric disorders: In a multicentre study of 247 people suffering from medication overuse headache, Radat et al. (2008) found that a history of migraine was a risk factor for the development of dependence on acute migraine treatments. A further study by Radat, Mekies, et al. (2008) amongst 5417 migraine patients showed how maladaptive coping combined with stress and impairment from migraine cause an escalation in psychopathology, with migraineurs progressing from no psychopathology to anxiety and finally concomitant anxiety and depression as the levels of the three mediators rise. Autret, Roux, Rimbaux-Lepage, Valade, and Debiais (2010) and Singh, Shukla, Trivedi, and Singh (2013), have shown correlations between migraine and depression and anxiety.

In order to investigate possible patterns in the psychological, behavioural and socio-environmental factors associated with primary headaches, Kröner-Herwig and Gassmann,

(2012) compared 2132 children with primary headaches with 1267 healthy children in the Southern Lower Saxony region in Germany. Migraine sufferers made up 7.8% of the cohort ($n = 314$). Maladaptive psychological traits were particularly significant risk factors for migraine and both negative psychological variables and socio-environmental stressors were more strongly associated with migraine than tension type headache.

Lake (2009) describes two forms of dysfunctional or maladaptive pain coping amongst headache sufferers, namely sensitising (hypervigilance and anticipating, catastrophising and hyperempathy) and minimising (alexithymia, stoicism, denial or anger suppression). Pain catastrophizing is a particularly prominent coping strategy amongst migraine sufferers (Abbate-Daga et al., 2007; Chiros & O'Brien, 2011; Thorn et al., 2007). Migraine sufferers also tend to suppress their anger, leading to internalised negative emotions (Abbate-Daga et al., 2007; Materazzo, Cathcart, & Pritchard, 2000). This catastrophizing and internalised anger may partly explain the occurrence of depression, substance abuse and anxiety in migraineurs. However, none of these studies claim to answer how these negative coping mechanisms evolved.

2.5 Conclusion of Chapter 2

When trying to understand the phenomenon of MO, it is not easy to avoid the political arguments that have arisen around its diagnosis. Most importantly for this study, one cannot ignore the challenges of using multiple laboratory tests to confirm and exclude symptoms in a large cohort. Though only reliant on self-report, the case definition for MO in this study requires that various other headache sub-forms are ruled out. However, migraine remains a complex disorder and unpacking its causes has not been easy for researchers, many of whom consider that both biological and psychosocial determinants are involved and urge a biopsychosocial approach to migraine research.

Chapter 3: The Biopsychosocial Approach

This chapter deals with the theoretical framework for the study, George Engel's biopsychosocial approach. The aim of this discussion is to provide sufficient background on the biopsychosocial framework to help map the central outcome concept for the research (HRQOL in MO) within this frame. The chapter begins with the rationale for choosing a biopsychosocial frame. This is followed by a description of Engel's main points on the framework and then critiques thereof.

3.1 Rationale for choice of this framework

The theoretical framework chosen to guide this journey is based on Engel's Biopsychosocial Model. Though the biopsychosocial framework was originally proposed as a means of re-imagining psychiatric treatment, its use in this thesis is considered a pragmatic approach toward the integration of various forms of inquiry around HRQOL. This is because the biopsychosocial framework work has been adapted to inform a research framework that has been useful in guiding inquiry into multidisciplinary fields of health and disease - pain in particular (Andrasik, Flor, & Turk, 2005; Gatchel & Turk, 2008; Gatchel, 2004; Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Lumley et al., 2011). This led to the starting point for this thesis - the assumption that HRQOL in MO may be better understood through a process of inquiry that examines various systems of a migraine patient's life and allows for the integration of biological and psychological methods in order to do so.

The interdisciplinary nature of this study arose from curiosity around emotional, cognitive and behavioural aspects of migraine: Social scientist may be interested in how MO symptoms manifest in our society and how this impacts HRQOL (which relates to the first aim of this study). Physiologists want to know which neurobiological systems contribute to the subjective experience of HRQOL in pain (the second aim). Psychologists want to explore which factors of a MO's sufferers life contribute to HRQOL, so that the best focus can be

found for interventions (this is linked to the third and final aim). These questions represent three facets of the attempt to build an integrated understanding of HRQOL in migraine as the researcher progresses on a journey to becoming a neuroscientist.

While the biopsychosocial approach was followed in this study as an approach to inquiry, biopsychosocial approaches have also been used in clinical practice. A clear formulation of the patient's needs can lead to improved patient-clinician communication (Borrell-Carrió et al., 2004). There is evidence to suggest that a biopsychosocial treatment approach is at least moderately effective in treating pain (Vowles & McCracken, 2008). More recent models, such as the Functional Model of Headache, indicate that headache sufferers may benefit from treatments such as stress coping or couples therapy (Martin, 2008). Thus, a combination of biological and psychosocial approaches may be most beneficial to the patient.

3.2 George Engel's proposal

In his model, Engel posited that biological activities, psychological events and social behaviours are interrelated in their involvement in health and illness (Suls & Rothman, 2004). In his paper titled: "*The need for a new medical model: A challenge for biomedicine*", Engel (1977) criticised the adherence of psychiatry to what he viewed as a flawed model of disease, the dominant biomedical model. In the biomedical model's place, Engel put forward an understanding of disease, which embraced the social, behavioural and psychological, as well as the biochemical elements of the patient (Engel, 1977; Smith & Strain, 2002). He claimed that treatment could be improved by considering these four elements in combination, rather than simply isolating the physiochemical factors of disease (Smith & Strain, 2002).

Essentially, Engel rejected the reductionist and dualistic nature of the biomedical model (McLaren, 1998); arguing that it had become dogma and propagated exclusionary sentiments that placed mental illness in the category of myth simply because its origin was not always clearly biochemical. Engel's main criticism of the biomedical model can be viewed

as two-fold (Borrell-Carrió, Suchman, & Epstein, 2004; Gatchel et al., 2007; Lumley et al., 2011):

1. The exclusion of subjectivity from study: Engel effectively took a systems perspective of disease and health, in which the view of the patient is incorporated into the understanding of the context (Borrell-Carrió et al., 2004). This conflicted with the biomedical model in which the health practitioner's view of the context was considered truth. Furthermore, Engel criticised the way in which practitioners ignored the influence of the observer on the observed. Borrowing again from systems theory, Engel encouraged practitioners to be mindful of how their behaviours contributed to the occurrence, worsening or improvement of symptoms (Engel, 1977).
2. The blanket application of dualism and reductionism: The unyielding devotion to dualism in the biomedical model led to the reductionist belief that disease is either caused by the physical or the psychological and that these two processes are discrete (Gatchel, 2004; Lumley et al., 2011). Sadly, this contributed to the reduction of all disease to a physiological explanation and the relegation of all psychological problems to a position of diminished usefulness. The perception then prevailed that, without a physiological cause, an illness was not real. In the case of pain that could not be conclusively linked to physiological change, the pain was seen as malingering or sustained through reinforcement (Andrasik, Flor, & Turk, 2005).

In contrast, biopsychosocial perspective considers multidirectional relationships between physiological, behavioural and environmental factors (both physical and social) in disease (Nicholson, Houle, Rhudy, Norton, & Forest, 2007). This shifts the emphasis from the discussion of linear relationships to the use of linear approximations to understand circular causality in disease (Borrell-Carrió et al., 2004). Such reasoning marks a shift from the

"unidirectional, oversimplified" (Andrasik et al., 2005, p.87) models of pain in general, and of headache in particular.

Engel based his model on von Bertalanffy's general systems theory, believing that general systems theory would allow psychiatrists to examine various levels of the patient's life. Therefore, central to Engel was the premise that "Nothing exists in isolation. Whether a cell or a person, every system is influenced by the configuration of the systems of which it is a part, that is by its environment" (Engel, 1980, p. 537).

Engel (1980) arranged the human system into various levels, which he viewed as both hierarchical and continuous. These system levels are: molecule, cell, tissue, organ / organ system, nervous system, individual, dyad, family, community, culture -subculture, society-nation, biosphere. Within a hierarchy, each level represents a distinct and complex integrated whole, requiring unique methods for being understood. As a continuum, each component of the system is also part of a higher level. In this way one can understand the individual as distinct from, and yet, part of a larger social system (Engel, 1980).

Engel's levels and how they link to this thesis are shown in Figure 3.1. In the current research, all levels in Engel's work are used to examine HRQOL in MO, except the biosphere. The biosphere is omitted because there is little information on what this level entails practically in research. At the most fundamental level represented in the current thesis is the molecular wherein lies the examination of the serum concentration of glutamate and an examination of its transporter expression. This is followed by exploration of the individual's behaviour with reference to his / her temperament and coping strategies. The subject's interactions with those outside self (interpersonal relationships in terms of dyadic, family and community interactions) fit with the exploration of perceived social support. Although not prominently featured, the wider lifestyle behaviours (smoking and alcohol consumption) that are accepted in society are addressed in the analysis.

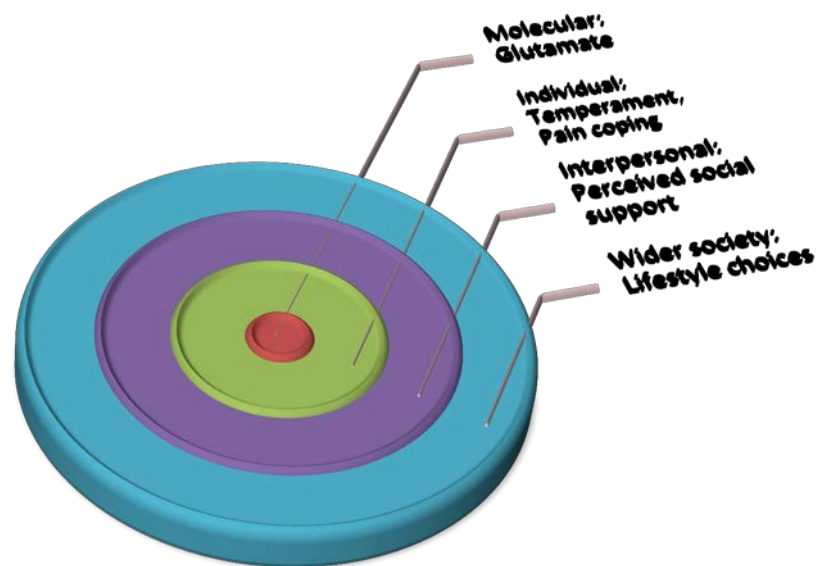


Figure 3-1: The levels of investigation for this study, in accordance with Engel’s Biopsychosocial Model

At this point it may be useful to make explicit two points about the application of the Biopsychosocial Model in this thesis. The first being that there has been a transition from viewing the Biopsychosocial Model in the context of psychiatry to seeing the success and possibilities for the application of the *approach* in research. For some this is a natural and logical progression that hardly warrants mention. However, it is important to acknowledge that Engel’s work has a much wider application outside of psychiatric formulation. The second point relates to the use of the term “Biopsychosocial Model” versus “biopsychosocial approach”. The former refers to the original theory posited by Engel. The latter meanwhile, indicates the broader application of the theory and also acknowledges that there are multiple iterations of Engel’s work that have evolved into multiple branches of inquiry, such as psychoneuroimmunology (Irwin, 2008; Lutgendorf & Costanzo, 2003; Schleifer, Marbach, & Keller, 1990); mind-body medicine; psychophysiology (Andrasik, 2006; Corr & Perkins, 2006; Mangina, 2009; Ong, Gramling, Vrana, Nicholson, & Buenaver, 2006); behavioural,

social and neurogenetics (Lee & Tracey, 2013; Slavich & Cole, 2013) and psychopharmacology (C. E. Dean, 2011; Nutt & Lingford-Hughes, 2004).

3.2.1 Criticism of the Biopsychosocial Model.

In the three decades since its inception, the Biopsychosocial Model has had its share of detractors alongside its supporters. The criticisms levelled at Engel's work relate chiefly to its similarity to older models and whether or not it is actually useful.

Blueprint or carbon copy?

Engel described his work as a "blueprint for research, a framework for teaching, and a design for action in the real world of health care" (Engel, 1977, p.135). Critics have argued that Engel's work is not original; for some, the Biopsychosocial Model bears too close a resemblance to Meyer's Psychobiology (Ghaemi, 2009; McHugh, 1992; G. C. Smith & Strain, 2002). Ghaemi goes as far as to describe the Biopsychosocial Model as nothing more than eclecticism and attributed much of the theory (including the name) to Roy Grinker whose work appeared some 25 years before Engel's.

Schwartz (1982) lends some perspective to this criticism: Engel and many other theorists whose works have given rise to interdisciplinary behavioural medicine were products of a growing paradigm shift toward synthesis. Schwartz (1982) locates the origin of this zeitgeist in Canon's work on stress, which implanted homeostasis as a consideration in psychology and sociology and not only medicine. Engel himself did acknowledge the influence of other theorists such as von Bertalanffy, Meyer and Mead on his work (Engel, 1977), though Grinker's name is notably absent.

More or less useful?

In examining the validity of the Biopsychosocial Model in modern psychiatry, Ghaemi (2009) argues strongly that Engel's work has promoted the damaging effects of the eclecticism that ails the profession. He construes the Biopsychosocial Model as embodying

the unavoidable lack of boundaries inherent in eclectic thinking. Ghaemi predicts that “...eclectic views cannot survive careful theoretical or scientific analysis” (2009, p. 26) because they are too unfocused and eloquently argues that research success lies in the ability to focus. However, his argument fails to take into account that, while there is the potential for drowning in data by including too much in a biopsychosocial study, even the study with few variables runs this same risk if the researcher does not pay attention to the initial question(s).

In response to the criticism that the Biopsychosocial Model attempts to incorporate too much information and thereby complicates questions, it is useful to note that, while Occam’s Razor may favour simplicity as the goal, it does not place simplicity as the paragon of accuracy (Domingos, 1999). Some questions have complicated answers. The exploration of the interconnectedness of systems of HRQOL in MO through a biopsychosocial approach might yield rich avenues for management of the disorder because the investigations of discrete areas of MO (genetic, physiological, pharmacological, etc) have brought us to a point of consolidation in the form of interdisciplinary research questions and approaches. In allowing for the possibility of multiple factors being involved in migraine, researchers now move to a time of trying to understand how these interplaying factors influence the system’s HRQOL. Earlier approaches to the study of migraine have already yielded numerous correlations between myriad variables. Continuing to study discrete parts of the migraineur’s subsystems is likely counterproductive, while testing the hypothesized relationships between these various factors and their (biological, psychological and social) domains may provide the metaperspective necessary to push migraine HRQOL research further forward. As Gatchel and Turk (2008, p.12) explain: “The fact that a Biopsychosocial Model requires a better understanding of the complex interaction of a number of factors does not make it untenable... We are still at the infancy stage in developing complex solutions for complex problems”.

Simply pragmatic?

Engel insisted that the Biopsychosocial Model was a scientific model for achieving real world solutions in health care (Engel, 1980; Engel, 1977). It is at this juncture that critics argue that Engel did not provide enough detail as to how the Biopsychosocial Model was to be applied. For McHugh, Engel's descriptions are too non-specific to relate to any one particular disease. McHugh believes that the Biopsychosocial Model lacks the necessary structure and definitive rules to allow for disease categorisation (McHugh, 1992). One glaring deficiency is seen in Engel's neglect of detail on the biosphere, which was mentioned earlier in this chapter.

Much of these arguments are communicated in McLaren's (1998) question: Is the Biopsychosocial Model in fact a model? McLaren is accurate in stating that the work does not meet the requirements of being called a scientific model, but it has enough to recommend it as a theoretical framework for guiding research - especially if one reads it as a pragmatic approach.

Pragmatism in its early form is associated with the works of Charles Sanders Peirce, William James and John Dewey. James describes pragmatism as a method for clarifying concepts. For James (1981), pragmatism "...unstiffens' our theories... has no prejudices whatever, no obstructive dogmas, no rigid canons of what shall count as proof." (p. 79). The essence of pragmatism is bound in the maxim that the value of a theory is derived from the fruits of its application (James, 1981; Liszka, 2012), or how useful it is within the context of the inquiry and taking into account the researcher's goal (Long, 2013). Pragmatism acknowledges the fallibility of all methods, but places empiricism at the centre of knowledge acquisition (Dewey, 1905; Long, 2013).

Lewis (2008) reiterates both Engel's desire for the Biopsychosocial Model to be a blueprint for research and McLaren's view that the model never had the scientific underpinning required to reach this goal. Lewis then points out that the model has not

remained static since its inception and proposes a pragmatist re-interpretation of the Biopsychosocial Model as a logical step to allowing the integrated study of biology and psychology, without setting illogical limitations on what can and cannot be studied.

Lewis (2008) counters the eclecticism arguments against the Biopsychosocial Model by pointing out that Dewey never advocated inquiry for inquiry's sake. Engel's work can then be seen as posited theory, as a point of departure (in this case a conceptual model) placed in public space for critique and improvement. This means that it is defensible to use various forms of the scientific method, with the understanding that each system may have a different language and warrant different methods of inquiry.

Within the context of inquiry into a multifaceted concept such as HRQOL (or, indeed, MO), the strength of the biopsychosocial approach really lies in its appreciation of the complexity of human health and disease. Acknowledgement is given to the effects of the various systems of the individual - from the molecular to the societal (Borrell-Carrió et al., 2004). This presents the researcher with the challenges of questioning reductionist approaches to disease and building dialogue between objective measures of illness and health and subjective experiences of the patient (Borrell-Carrió et al., 2004). As Bourke (2013) states: "Pain does not emerge naturally from physiological processes, but in negotiation with social worlds" (p. 155) and understanding how patients make sense of their headache using the physiological and psychosocial can help advance us from a blaming position to respectful inquiry (Cecchin, 1987). This is not a new notion: In 1982 Loeser put forward a model of pain that included examination of the suffering (the emotional response) and the pain behaviour (overt communications of pain) of the patient. Waddell then underscored the importance of Loeser's inclusion of these two dimensions when, in 1987, he suggested that a full conception of pain requires comprehension of the person exposed to the pain (Gatchel et al., 2007).

In Chapter 2 the major determinants of migraine put forward in the literature were already reviewed. Extensive research indicates that there are potential biological and

psychosocial determinants of the disorder: Temperament, coping, social support, adverse early life events, coping and stress are prominent psychological markers in migraine, while glutamate has emerged as a strong biomarker for the disorder. There is reasonable expectation that a biopsychosocial approach may assist in our understanding of how these concepts fit together in MO as it has already been a useful approach in chronic pain assessment and intervention in osteoarthritis, fibromyalgia, rheumatoid arthritis, temporomandibular joint pain disorders, shoulder pain and even multiple sclerosis (George et al., 2008; Kerns, Kassirer, & Otis, 2002; Oliveira et al., 2009; Suvinen, Reade, Kemppainen, Könönen, & Dworkin, 2005). Biopsychosocial pain research has contributed to some of the most significant shifts in our conceptualisations of pain. Most notably, there has been movement from dualist and reductionist models towards more integrated theories through the acceptance that diversity in signs and symptoms of an illness can be the result of intricate interconnections of an individual's predispositions, biology, psychology, sociocultural environment; perception and response to illness and changes in these states (Andrasik et al., 2005; Andrasik, Buse, & Grazzi, 2009; Van Eeghem, 2005).

Martin (2007) reminds us that it is the vulnerability to migraine that is inherited and even with such a predisposition, some individuals will not suffer from the headache. In short: Biology cannot be viewed in isolation from the psychosocial aspects of an individual's life. The implications of this assertion are far-reaching for MO research, as researchers are challenged to move away from the predominantly biomedical model of headaches and include psychosocial contexts in their investigations. Andrasik et al. (2005) argue that a biopsychosocial approach to understanding head pain acknowledges the complex interactions of biological, psychological and social factors in the diverse presentation of and the individual response to headaches. Including psychosocial alongside biological factors is necessary for accurate understanding that can lead to improved treatments for migraine (Andrasik et al., 2005; Sieberg, Huguet, von Baeyer, & Seshia, 2012). The use of a biopsychosocial frame for

migraine studies has also been supported by Newton (2008). Meanwhile, Andrasik et al. (2009) have suggested that migraine be characterised as a biobehavioral disorder (a disorder constructed through links between biological, psychological and environmental aspects).

Shifts toward a biopsychosocial frame of examining pain have already led to important discoveries regarding headache (Kröner-Herwig, Morris, & Heinrich, 2008; Nicholson, Hursey, & Nash, 2005). In particular, biopsychosocial research has shown the usefulness of biobehavioural interventions in migraine (Andrasik et al., 2009; Van Eeghem, 2005); enhanced our understanding of how migraine is triggered (Hashizume et al., 2008) and sensitized the world about how severely migraine impacts HRQOL (Leonardi et al., 2010; Napolitano, 2008).

3.3 Today's challenge

Reflecting on the history of migraine in research, the overall depiction is one of a fragmented approach in which no single theory has unlocked a comprehensive understanding of the headache. In addition, there has been a heavy emphasis on biomedical theories, with little or no reference to the role of the psychological and the social worlds in aetiology.

The two dominant, divergent views of migraine as having either a neurological origin with vascular changes as secondary - the neural hypothesis (Blau, 1984) – or being the result of a primary neurovascular pathology, have persisted, and researchers have struggled to move into more integrated frameworks for explaining migraine. Some traction has been gained through the consideration that migraine may be a multifactorial disorder that is part of systemic rather than localised dysfunction (Loder et al., 2006). The challenge now appears to lie in conceding the involvement of psychosocial determinants (Andrasik, Flor, & Turk, 2005). Arguments for a biopsychosocial approach to this research are examined in the following chapter.

3.4 Conclusion of Chapter 3

This study is guided by the principles of Engel's Biopsychosocial Model. Though criticized as not meeting the criteria for a model, the principles of the work are valuable as a guiding approach to research – in particular because they value the subjective view of the patient. In this thesis, the HRQOL of MO sufferers is examined from the molecular to the wider societal levels through investigations of glutamate, temperament, coping, social support and lifestyle.

The call for biopsychosocial approaches to MO research has been influenced in part by the important contributions of similar studies in various pain disorders. Recent significant findings related to migraine using the biopsychosocial approach have highlighted its potential usefulness and promoted its application in this thesis.

At this point it becomes necessary to start discussing how the biopsychosocial approach relates to the key concepts of this research. HRQOL has been chosen as the point of departure for this discussion as it is the main outcome variable measured in the study.

Chapter 4: Health-Related Quality of Life in a Biopsychosocial Framework

Following the discussion of the biopsychosocial framework in the previous chapter, in this chapter how health-related quality of life (HRQOL) is constructed within a biopsychosocial framework is examined. The chapter then shifts focus to a discussion of the findings about the HRQOL of people suffering from migraine and which biological and psychosocial variables have been proposed as role-players in HRQOL in migraine. Drawing together this information, an argument is put forward for the inclusion of glutamate neurotransmission, temperament, pain coping and perceived social support in the examination of HRQOL in MO.

4.1 Quality of Life and Health-Related Quality of Life

Though the idea of “a life of quality” (Schalock, 1994, p. 266) is an ancient one, defining, conceptualising and operationalising quality of life (QOL) is not easy. Debate persists amongst a number of researchers (Holm, Holst, & Perl, 1994; Kuehn & McClain, 1994; Schalock, 1994; Wolfensberger, 1994), not least because QOL has been described using many terms, including well-being, life satisfaction, positive self-concept, personal meaning, enjoyment of life, improved social and environmental circumstances, the enhancement of one’s various domains of life and the meeting of one’s needs (Brown & Brown, 2003; Goode, 1994; Holm et al., 1994; Kerce, 1992). While these are not necessarily disparate definitions of QOL, they are broad and perhaps more than just a little unwieldy. Moreover, these ideas are not easy to measure and research.

The concept of HRQOL reflects a narrowing of the wider concept of QOL to focus on “the impact of disease and treatment on the lives of patients” (Wood-Dauphinee, 1999, p. 356). This was again widened a little to include the investigation of well-being and not only illness on the individual (Wood-Dauphinee, 1999). HRQOL is clearly defined by the Centers for Disease Control and Prevention (CDC) as those components of overall QOL that affect

mental or physical health (Centers for Disease Control and Prevention, 2011). For the purpose of this study, the term HRQOL is used in keeping with the CDC definition. A very simple distinction between QOL and HRQOL is provided by Ferrans (2005) who states that HRQOL deals with the impact of disease and treatment and is distinct from those aspects of life that are outside of the scope of healthcare, such as education and political freedom. This distinction may be a little simplistic though, and Ferrans does go on to acknowledge that some non-HRQOL factors can become health-related. For example, a lack of education can affect hygiene practices and lead to infection of a wound. The distinction is therefore not solid.

An aspect of HRQOL research that the reader should take into account is that QOL and HRQOL are often used interchangeably, leading to confusion. Wolfensberger (1994) is highly critical of the way in which terminology is misused in QOL writings, but the practice continues and perpetuates the difficulty in clearly defining QOL. Some publications claiming to deal with QOL actually investigate HRQOL (e.g. Benedict et al., 2005; Ordu Gokkaya et al., 2012) or even perceived health status while claiming to investigate QOL (Moons, 2004). A concerted effort has been made to point out which concept is being discussed in the literature reviewed in this thesis and to keep the use of QOL and HRQOL separate to avoid confusion.

4.1.1 Measuring health-related quality of life.

In the 1970s practice began to shift from the exclusive use of clinical and laboratory measures to characterise disease to incorporating aspects of the patient's subjective experience (Schalock et al., 2002; Wood-Dauphinee, 1999). This intensified the need for formal measures to examine changes in QOL. An important research milestone was reached in 1977, when QOL became a key word on the Medical Subject Headings of the United States National Library of Medicine MEDLINE Computer Search System and reference to QOL grew from 40 in the 1970's to over ten thousand between 1986 and 1994 (Wood-Dauphinee,

1999). This exponential rise in research on QOL also reflected a growth in the measures of both overall QOL and HRQOL – not all of which are of desired quality (Taillefer, Dupuis, Roberge, & Le May, 2003).

For Ferrans (2005) it is important to acknowledge that HRQOL, like QOL, is a multidimensional construct. The domains of HRQOL are usually noted as physical, mental and social, but also can include economic and spiritual domains (Ferrans, 2005; Wood-Dauphinee, 1999). Many of the instruments used to measure HRQOL reflect these domain variations.

There are a number of general HRQOL measures, such as the various Short Form (SF) formats. The SF-36 was developed as part of the Medical Outcomes Study (MOS). The MOS was a multi-year study of patients with chronic illnesses, which was designed to explore the differences in patient outcomes and to create tools for monitoring patients effectively (Tarlov et al., 1989; Ware, 2004). In designing the SF scale, the researchers used the following domains: Limitations in physical activities because of health problems; limitations in social activities because of physical or emotional problems; limitations in usual role activities because of physical health problems; bodily pain; general mental health (psychological distress and well-being); limitations in usual role activities because of emotional problems; vitality (energy and fatigue) and general health perceptions (Ware, 2004; Ware & Sherbourne, 1992). Progressively shorter versions of the SF have been released and used in previous headache studies (Brna et al., 2006; Brna, Gordon, & Dooley, 2008; Fuh & Wang, 2006; Lipton, Hamelsky, Kolodner, Steiner, & Stewart, 2000; Rubino et al., 2013; Sharma, Singh, & Remanan, 2013; Wang, Fuh, Lu, & Juang, 2001).

The measurement of HRQOL is as varied across studies as the illnesses investigated. Though some researchers rely on measures of symptoms (or their absence) or treatment recidivism, neither of these are extremely good markers of health (Becker, Diamond, & Sainfort, 2011) and illness-specific measures of HRQOL have therefore been developed.

Factors such as specificity (e.g., to a specific aspect of a disease), generalisability, culture, cost, accessibility and literacy levels have all added to the development of new measures or variations on previous measures. In her comprehensive review of scales to measure disease, Bowling (2001) lists no fewer than a dozen HRQOL scales specific to psychological health; she discusses numerous other HRQOL scales specific to cancer, respiratory, neurological, rheumatological, cardiovascular and other diseases. Given that this is a comparative study, the choice was made to use a general HRQOL measure rather than a migraine-specific measure such as the Migraine-Specific Quality of Life Questionnaire (Martin et al., 2000).

According to Higginson and Carr (2001), there are eight uses for HRQOL measures in practice, namely to: Rank problems, smooth communication, assess for possible complications, identify preferences, examine changes or treatment reactions and train new staff. The authors argue that the introduction of measures of the patients' perspectives on their illness is justified as no illness is divorced from the individual's social and individual context. Researchers clearly agree with the usefulness of HRQOL measurement and there is widespread use of HRQOL measures in examining *inter alia* the outcomes of people with mental illness (Becker, Diamond, & Sainfort, 2011), undergoing dialysis (Chan et al., 2012; Østhus et al., 2012), suffering from pain (Kolotylo & Broome, 2000; Nickel et al., 2008; Ostberg & Hall-Lord, 2011) and cancer (Hwang, Chang, & Kasimis, 2002; Stephens, 1998).

Over the past four decades, a number of research consortiums have arisen to investigate QOL and HRQOL, many of which use different measures. These include the World Health Organisation's working group, WHOQOL, the International Society for Quality of Life Research (ISOQOL) and the European Quality of Life group, EuroQoL and a number of disease-specific entities such as the European Organization for Research and Treatment of Cancer (EORTC).

4.2 Health-Related Quality of Life in Migraine

Migraine is considered a significant burden on the sufferer's HRQOL (Hazard, Munakata, Bigal, Rupnow, & Lipton, 2009; Raggi et al., 2012). The WHO has recognised this as a serious public health challenge (World Health Organization, 2012).

HRQOL is fairly poor for migraine sufferers and falls below that of the general population and of people suffering from epilepsy and arthritis (Aydemir, Ozkara, et al., 2011; Brown et al., 2008). Significantly impaired HRQOL in migraine is a constant feature across a number of countries (Bera et al., 2014; Leonardi et al., 2010). One of the largest cross-country studies on migraine HRQOL is the International Burden of Migraine Study. This study made use of survey data from 10 countries (Australia, Brazil, Canada, France, Germany, Italy, Spain, Taiwan, the United Kingdom and the United States of America) and had a total sample of $N = 23\ 312$. The study made use of the Migraine-Specific Quality of Life Scale (MSQ), with results indicating that chronic migraine sufferers had a significantly lower HRQOL than episodic sufferers ($p < .0001$). Comparison with other illness populations shows that migraine has a considerable impact on daily living (Aydemir, Ozkara, et al., 2011; Brown et al., 2008; Dalhof & Dimenas, 1995). This is not surprising given the frequency with which attacks occur: A multi-site survey of 150 migraine patients in the United States, showed that the mean monthly frequency of attack was 4.4 ± 3.6 , with 20% of patients experiencing more than six attacks per month (Brown et al., 2008).

4.2.1 Popular models of health-related quality of life and the biopsychosocial approach.

A number of models of HRQOL have been proposed and many reflect similar components, domains and determinants. For Taillefer et al. (2003) there are concerns around the lack of sophistication and evaluation of these many models. A considerable number of models for HRQOL has been generated in the field of disabilities (Brown & Brown, 2005; Goode, 1994; Kuehn & McClainm, 1994; Parmenter, 1994; Prehn et al., 2007; Schalock et al.,

2002); and in the economics of healthcare (Broome, 1995; Torrance & Feeny, 1989). Models have been generated for various age groups (Brown, Bowling, & Flynn, 2004; Kelley-Gillespie, 2009) and illnesses (Elliott & Richardson, 2014; Østhus et al., 2012; Parmenter, 1992).

Wilson and Cleary developed the Conceptual Model of HRQOL (Wilson & Cleary, 1995), in which they include four levels of variables that contribute to HRQOL. Wilson and Cleary posited that measures of health status could be conceptualised along a continuum that begins with simple biological and physiological factors, and moves through increasing complexity from symptoms to functioning to general health perception, and finally to HRQOL. These measures of health are influenced by individual and environmental characteristics and non-medical factors. Ferrans (2005) points out that the inclusion of values and symptoms in this model was a step forward in the inclusion of patient perceptions in HRQOL.

A revision of this model was attempted using relevant literature from 1985-2005 (Ferrans, Zerwic, Wilbur, & Larson, 2005). Figure 3.2 shows the original Conceptual Model (in blue) and the additions (in orange). The conceptual model was improved by the inclusion of more detailed explanations of the individual and environmental characteristics that influence HRQOL, based on McLeroy's ecological model. Ferrans and her colleagues explained that individual characteristics are viewed as intrapersonal factors, while environmental characteristics are made up of interpersonal factors (social support), institutional factors, community factors and public policy.

The Conceptual Model was arguably most thoroughly evaluated by Sousa and Kwok (2006). A sample of 917 HIV-positive patients drawn from the AIDS time-Oriented Health Outcomes Study (ATHOS) were evaluated for CD4 count, symptom status, functional status, general health perception and HRQOL. The measurement model fit the data adequately, while the structural model showed reasonable fit.

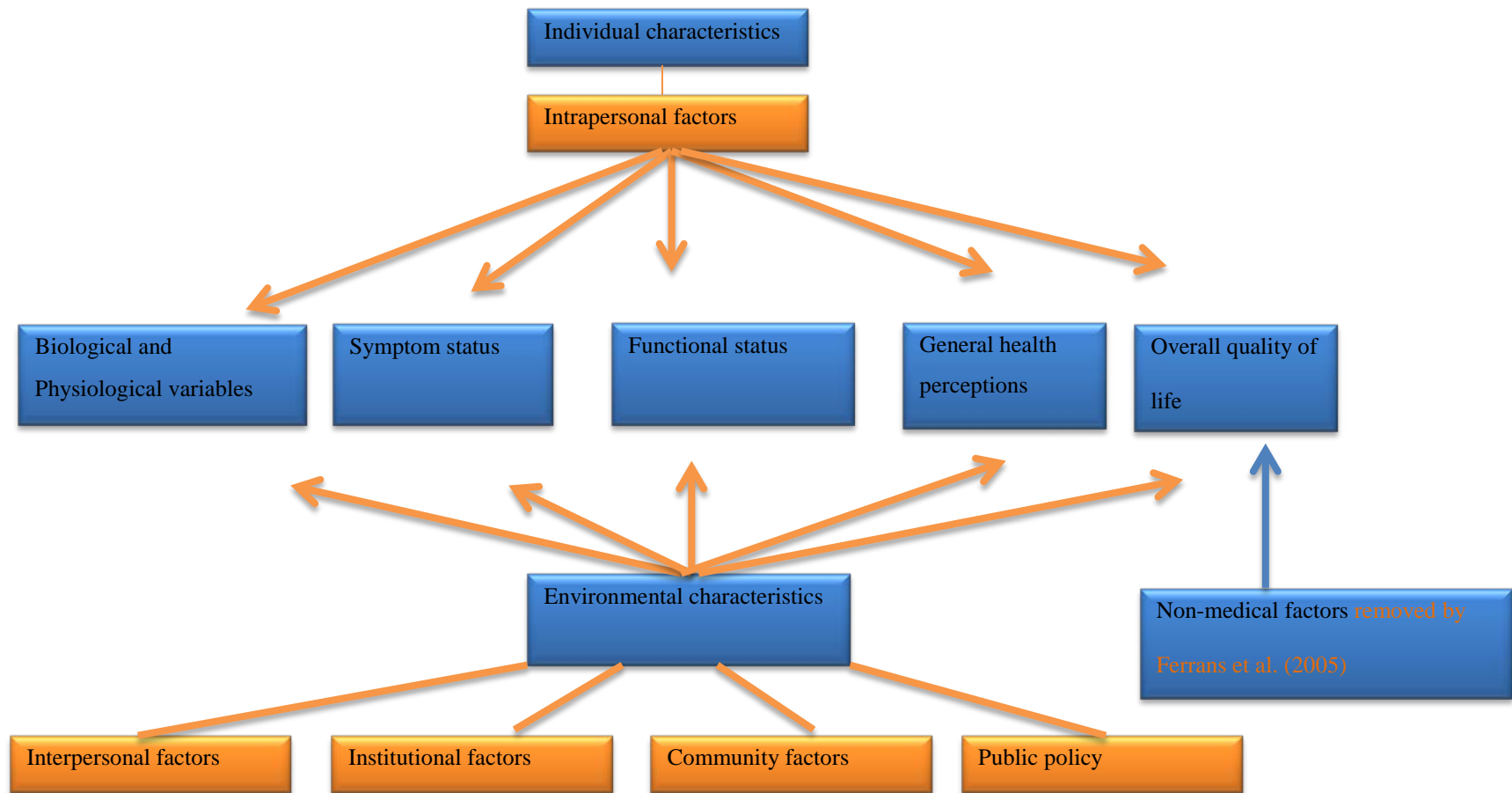


Figure 4-1 The revised conceptual model of health-related quality of life [adapted from Ferrans et al. (2005) and Wilson & Cleary (1995)]

A vast array of predictive models has also been generated in HRQOL (e.g. Ashing-Giwa, Tejero, Kim, Padilla, & Hellemann, 2007; Herrera Ponce, Barros Lezaeta, & Fernández Lorca, 2011; Kolotylo & Broome, 2000). Each model appears to be informed by the type of illness and the theoretical approach of the researcher. For example, in their investigation of HRQOL of patients with prostate cancer and their spouses, Kershaw et al. (2008) made use of a stress-coping framework to develop a model that considered antecedent factors, appraisal variables and coping strategies as predictors of HRQOL. The biological factors investigated included symptoms and disease phase, while psychosocial factors included self-efficacy, social support, hopelessness and coping style. Kershaw et al. found that patient HRQOL was adequately predicted by a model that included more active coping strategies; lower avoidant coping, hopelessness and baseline symptoms; less negative views of the illness and being newly diagnosed. Kershaw et al.'s work shows a significant role for psychosocial factors in HRQOL.

This is supported by the work by Ashing-Giwa, Tejero, Kim, Padilla, and Hellemann (2007). Ashing-Giwa and colleagues examined various predictive models of HRQOL in 703 patients with breast cancer. Their final model consisted of medical factors (such as stage of cancer), general health status, emotional wellness, demographics, health care system characteristics (e.g. level of accessibility), socio-ecological factors and ethnicity (listed separately from demographics as a cultural factor). This model predicted 70% of the variance of HRQOL.

Critique and the way forward for this research.

In their review of English-language articles published in PubMed, MEDLINE, CINAHL, and PsychINFO between 1999 and 2010, Bakas et al. (2012) found that the original Conceptual Model to be the most widely used HRQOL model, with the revision by Ferrans and colleagues emerging as a guideline for comprehensive HRQOL research. Despite such

wide use, the authors note that there had only been a single randomized controlled trial that employed the Conceptual Model. In addition, the authors found that the many models generated in HRQOL have not been thoroughly assessed. They advocated for more experimental work to refine these models in order to develop consensus and advance the field. This sentiment is shared by Nuamah, Cooley, Fawcett, & McCorkle (1999).

Essentially, there is no single HRQOL model to fit every person. The many predictive models – and even the conceptual ones - are based on the premise that understanding HRQOL requires a clear understanding of the individual's systems (Kuehn & McClainm, 1994). Both psychosocial and biological factors are taken into account in this understanding of the individual's systems, thus there is a strong case for viewing HRQOL within a biopsychosocial framework. Various predictive models in HRQOL also appear to include both biological and psychosocial elements to good effect. It was therefore considered justifiable to utilise a biopsychosocial approach to HRQOL in this research.

An obvious dilemma in HRQOL research –even when guided by a model – is that researchers are left with a wide array of factors to consider and corresponding measurements from which to choose. Utilizing existing research to guide decisions, this research drew on findings from migraine and other illness HRQOL studies, as well as HRQOL studies of ageing populations to propose which factors to investigate in MO HRQOL. These are discussed in the following sections.

4.2.2 Determinants / predictors of HRQOL.

Various studies have investigated a broad range of biological and psychosocial determinants of HRQOL and the results are highly variable across age (Ordu Gokkaya et al., 2012; Tajvar, Arab, & Montazeri, 2008) and the type of illness investigated. The latter includes studies of metabolic disorders (Vilhena et al., 2014), stroke (Carod-Artal, Stieven Trizotto, Ferreira Coral, & Menezes Moreira, 2009), cancer (Kenzik, Huang, Rizzo,

Shenkman, & Wingard, 2015; Nuamah et al., 1999; Perlis et al., 2014), epilepsy (Au et al., 2002; Aydemir, Özkara, et al., 2011; Elliott & Richardson, 2014; Luoni et al., 2011), renal disease (Chan et al., 2012; Østhus et al., 2012), traumatic brain injury (Nestvold & Stavem, 2009) and schizophrenia (Ho, Chiu, Lo, & Yiu, 2010; Ritsner, Gibel, & Ratner, 2006).

In searching for literature reviews on predictors of HRQOL (no specified dates entered on PubMed with the search terms predictor HRQOL, predictor / determinant “migraine HRQOL”; predictor / determinant “migraine QOL”; determinant / predictor "migraine-specific quality of life"), a few particularly informative reviews were located. These are summarised in Table 3.1. From these reviews a pattern emerges of the potential predictors of HRQOL. This pattern shows that both biological and psychological factors are potential determinants of HRQOL. Each determinant is discussed with reference to its review, followed by evidence from migraine studies.

Interestingly, only two reviews were listed in the initial search pertaining specifically to migraine HRQOL (Lucas, Geraud, Valade, Chautad, & Lanteri-Minet, 2006; Santanello, Davies, Allen, Kramer, & Lipton, 2002) and another one relating to primary headaches (Abu Bakar et al., 2016). On further investigation it was noted that the work by Lucas et al. is actually an empirical study and not a review.

Biological determinants.

The biological predictors identified in the reviews are mainly disease-related biomarkers (Ross et al., 2003; Spiegel, Melmed, Robbins, & Esrailian, 2008), with some clinical markers also represented (Abu Bakar et al., 2016; Pragodpol & Ryan, 2013; Soh, Morris, & McGinley, 2011). Since not all biomarkers are pathognomonic, some biological and clinical predictors may overlap in various illnesses (markers of low-grade inflammation are possible candidates here) and may thus emerge as predictors of HRQOL across a few disorders.

In addition, not all disease-specific markers evaluated emerged as significant determinants. For Spiegel et al. (2008) it was surprising that mineral metabolism and inflammatory markers were not significant determinants of HRQOL in end-stage renal disease (ESRD). In reflecting on potential biomarkers for HRQOL in MO then, it does seem as though including a biomarker for the disorder is prudent. A full account of the role of glutamate as a biomarker for MO was presented in Chapter 2. Since glutamate is emerging as a promising role-player in MO pathophysiology (Andreou & Goadsby, 2011; Freilinger et al., 2013; Lampl et al., 1999; Sarchielli, Di Filippo, et al., 2007; Vaccaro et al., 2007), it was hypothesised that investigating its role in MO HRQOL could provide important information.

Comorbid mental illness / negative affect/affective distress.

Psychiatric conditions were frequently found to be determinants of HRQOL across the reviews, with anxiety and depression being most frequently mentioned (e.g. Chang, 2004; Pragodpol & Ryan, 2013; Soh et al., 2011; Taylor et al., 2011). The relationship between mental illness and the HRQOL in migraine has been illustrated in various studies (Aydemir, Özkara, et al., 2011; Bera et al., 2014; Brna et al., 2006, 2008; Lantéri-Minet, Radat, Chautard, & Lucas, 2005; Mula et al., 2009; Raggi et al., 2012; Sharma et al., 2013). Though in their investigation of QOL of 40 patients with migraine and tension type headache, Bera, Goyal, Khandelwal, and Sood (2014) found that depression emerged as the most prevalent psychiatric problem amongst all headache sufferers, this prevalence was not significantly different from that of controls. This does not necessarily discount depression as a determinant in migraine HRQOL, but may indicate that depression is a general predictor across various illnesses.

Stress.

Another determinant identified in the reviews was stress - either daily stress or that resulting from early life adverse events (e.g. Chang, 2004; Cornish et al., 2009). In an

investigation of perceived stress and coping in 20 migraine and 20 tension type headache patients in Pakistan, Najam and Aslam (2010) made use of the Perceived Stress Scale, the McGill Pain Questionnaire and the Brief Cope Scale. The authors found significant a negative relationship between perceived stress and avoidant coping ($r = -.42, p < .001$) and a significant positive relationship between perceived stress and active coping ($r = .37, p < .001$). Though both relationships are only moderately strong, this does show that less effective coping strategies and perceived stress go hand in hand for migraineurs. Furthermore, perceived stress had a significant correlation with the affective pain reported by the participants ($r = .37, p < .001$), while higher coping strategy scores were correlated with lower evaluative pain ($r = -.27, p < .05$). Therefore, the higher the perceived stress experienced by the migraineur, the more likely he or she is to be employing avoidant coping strategies and experiencing pain.

Coping.

Coping emerged as a predictor of HRQOL in the reviews by Abu Bakar et al. (2016); Chang (2004); Cornish et al. (2009); and Sales, Carvalho, McIntyre, Pavlidis, and Hypantis (2014). However, each study reflects a different form of coping: Pain coping and maladaptive or poor coping.

Coping is defined as a person's mutable changing efforts to manage internal and external stressors (Chiros & O'Brien, 2011; Downing, Williams, Leserman, & Paulsen, 2013). Pain coping strategies include behaviours, cognitions and beliefs about pain; all of which have physiological consequences (Lake, 2009) and some of which are adaptive. Cognitions are self-statements about an event, while beliefs are pre-existing ideas about the nature of reality (Stroud, Thorn, Jensen, & Boothby, 2000). Negative pain cognitions and beliefs are associated with increased disability and distress (Stroud et al., 2000).

Lake (2009) describes two forms of dysfunctional or maladaptive pain coping amongst headache sufferers, namely sensitising (hypervigilance and anticipating, catastrophising and hyperempathy) and minimising (alexithymia, stoicism, denial or anger suppression). Lake also describes adaptive coping, such as the balanced use of distraction and body awareness, proactive coping, balanced interpersonal discussion of pain and pain acceptance.

There is evidence that various pain diagnostic groups are characterised by specific pain coping styles (Porter-Moffitt et al., 2006), with migraine being frequently associated with catastrophizing (Abbate-Daga et al., 2007; Chiros & O'Brien, 2011; Thorn et al., 2007). Catastrophizing is defined as a maladaptive strategy of coping in which an individual holds disproportionately negative cognitions about actual or expected pain (Lake, 2009). Catastrophizing usually presents with three features – rumination, magnification and helplessness (Lake, 2009; Sullivan et al., 2001).

Catastrophizing is an important aspect of migraine management as it can influence the decision to continue healthcare consultation (Lantéri-Minet et al., 2007). Holroyd, Drew, Cottrell, Romanek, and Heh (2007) explored catastrophizing, comorbid anxiety and depression and migraine characteristics in relation to migraine HRQOL in 232 frequent migraine sufferers. Catastrophizing and severity of migraine symptoms predicted HRQOL across the Migraine-Specific Quality of Life, Headache Disability Inventory, SF-36 and the Migraine Disability Assessment (β weights 0.16– 0.50, all $p < 0.01$), indicating that these two variables play an important predictive role in HRQOL of migraine sufferers.

Chiros and Brien (2011) examined catastrophizing alongside acceptance as forms of coping in migraine. They assessed 74 migraine patients on the Structured Diagnostic Interview for Headache, Chronic Pain Acceptance Questionnaire, Acceptance and Action Questionnaire, Pain Catastrophizing Scale and Chronic Pain Coping Inventory, while 60 participants also kept a daily diary. The findings show that higher levels of catastrophizing

were related to higher levels of daily pain ($t = 12.98, p < 0.001$). The research also indicated a role for pain acceptance in decreasing the amount of catastrophizing.

Pain / severity perception.

The subjective experience of pain or symptom severity is a determinant of HRQOL in migraine (Abu Bakar et al., 2016), gastrointestinal disorders (Chang, 2004) and epilepsy (Taylor et al., 2011). In a study of 102 migraine patients, mild to moderate correlations were indicated between HRQOL on the SF-36 and increased migraine severity (Leonardi, Raggi, Bussone, & D'Amico, 2010). Meanwhile, Kolotylo and Broome (2000) found that 65% of variance in HRQOL could be accounted for by depression, headache pain and chronic pain experience.

Personality.

The significance of personality in determining HRQOL was established in the study by Sales et al. (2014). In a selective overview of the psychiatric comorbidity in migraine and chronic daily headache sufferers, Pompili et al. (2009) made the point that the presence of psychiatric disorders are generally associated with lower QOL, resulting in poorer prognosis and response treatment as well as chronicity of headaches. They found that there has been relatively little research into personality disorders and headache. In fact, much of this research is around temperament and migraine, which is discussed in Chapter 2.

There are differences in temperament between migraine and other headache groups (Boz et al., 2004; Mazzone, Vitiello, Incorpora, & Mazzone, 2006) and particular temperament traits associated with migraine (Mazzone et al., 2006; Mongini, Fassino, et al., 2005; Sánchez-Román et al., 2007). Furthermore, temperament is related to HRQOL in migraine (De Filippis et al., 2008).

Social support.

The only social predictor to emerge from these reviews is social support (Cornish et al., 2009; Pragodpol & Ryan, 2013). Social support is essentially the resources provided by others (Swenson & Clinch, 2000), which can buffer against the impact of stress on psychological well-being (Skipstein, Janson, & Kjeldsen, 2012). According to Kitamura and colleagues (Kitamura et al., 1999), Barrera divided social support into two types - enacted and perceived. Enacted social support is the actual support that individuals receive from those around them. On the other hand, perceived social support is the resources that individuals believe will be available to them when needed. The latter has been correlated with better mental health (Kitamura et al., 1999).

Only one study could be identified that examines social support as a determinant of HRQOL in migraine. This study by Vos and Passchier (2003) showed that social support was an integral part of reducing the impact of migraine on daily life. However, this was a small study ($N = 48$) and limitations of sample size must be taken into account. Social support is an important aspect of migraine management (Peters et al., 2005), yet female migraine patients are more inclined to engage internal defence mechanisms than seek social support when faced with a challenge (Stronks et al., 1999). Thus, seeking social support is considered to be a form of active coping (Rueda & Rothbart, 2009).

In a study of 100 subjects, social support was one of the main factors associated with migraineurs consulting physicians about their headaches (Skomo, Desselle, & Berdine, 2006). Social support can therefore be an instrumental part of treatment amongst migraineurs. However, migraineurs tend to be less satisfied with the support they receive than non-headache counterparts (Martin & Soon, 1993).

Sociodemographics.

Sociodemographic and clinical factors that predict HRQOL are numerous and range from age, disease-specific risk factors and sex (e.g. Chang, 2004; Pragodpol & Ryan, 2013) to symptom severity (e.g. Abu Bakar et al., 2016) and the type of intervention employed (Santanello et al., 2002; Zainuldin, Mackey, & Alison, 2011). There do not appear to be clear indications of sociodemographic variables that predict HRQOL in migraine.

Treatment.

A study of the efficacy of homeopathic treatment of migraine in 53 patients indicated that such intervention significantly improves the HRQOL dimensions of bodily pain and vitality ($p < .0001$) after 4-6 months of treatment. The narrative review by D'Amico, Grazzi, Usai, Leonardi, and Raggi (2013) showed that migraine HRQOL is improved by various treatments, such as migraine symptomatic and prophylactic medication and surgery.

There are also numerous studies dealing with the efficacy of various medicines, including sumatriptan (Colman et al., 2001; Wendt, Cady, Singer, Peters, et al., 2006), rizatriptan (Santanello et al., 2002) and topiramate (Silberstein, Neto, Schmitt, & Jacobs, 2004). Santanello and colleagues reviewed the findings of two clinical trials on rizatriptan use in migraine (combined sample $N = 1506$). Headache recurrence and relief from symptoms and restoration of function at two hours, two were found to be associated with better migraine-specific HRQOL, as was rizatriptan intervention. This indicates a role for the evaluation of biological factors in migraine HRQOL.

Table 4-1: Summary of determinants of health-related quality of life identified in review articles

Citation	Identified determinant(s) of HRQOL
Quality of life in primary headache disorders : A review (Abu Bakar et al., 2016)	Headache characteristics: Pain intensity and duration Migraine-specific characteristics: Presence of nausea Other health characteristics: Health-related disability, comorbid pain conditions Psychological characteristics: Psychological response to pain, pain coping and psychiatric comorbidity
Determinants of migraine-specific quality of life (Santanello et al., 2002)	Migraine therapy
Critical review of factors predicting health-related quality of life in newly diagnosed coronary artery disease patients (Pragodpol & Ryan, 2013)	<i>Sociodemographic</i> Positive predictors: Baseline HRQOL, education, marital status Negative predictors: number of cardiovascular risks, female sex Inverse predictor: Age <i>Clinical</i> No positive or inverse predictors Negative predictors: Angina, physical functioning, fatigue <i>Psychosocial</i> Positive predictors: Social support, sense of coherence Negative predictors: Depression, anxiety and depression, overall psychosocial functioning or mood disturbance, anxiety, hostility
Optimal intensity and type of leg exercise training for people with chronic obstructive pulmonary disease (Zainuldin et al., 2011)	Exercise
The course and predictors of health-related quality of life in living kidney donors: A systematic review and meta-analysis (Wirken et al., 2015)	Low psychological functioning pre-donation
Determinants of health-related quality of life in Parkinson's disease: A systematic review (Soh et al., 2011)	Depression, motor symptoms, complications arising from treatment
Predictors of health-related quality of life and costs in adults with epilepsy: A systematic review (Taylor et al., 2011)	<i>Clinical</i> Seizure frequency, seizure severity <i>Psychological</i> Depression, anxiety Comorbidities
Psychosocial predictors of health outcomes in colorectal cancer: A comprehensive review (Sales et al., 2014)	<i>Clinical</i> Presence of a stoma

	<p><i>Psychological</i> Type D personality, Sense of Coherence, ego-specific defence mechanisms</p>
Associations between social support and stroke survivors' health-related quality of life - a systematic review (Kruithof, van Mierlo, Visser-Meily, van Heugten, & Post, 2013)	Social support
A systematic review evaluating health related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder (B. Dean, Gerner, & Gerner, 2004)	Bipolar disorder
The effect of anaemia treatment on selected health-related quality-of-life domains: a systematic review (Ross et al., 2003)	Haematocrit (Hct)
A systematic review of health-related quality of life in cutaneous melanoma (Cornish et al., 2009)	<p><i>Clinical</i> Health status (probably related to insomnia and pain) Systemic therapy</p> <p><i>Psychosocial</i> Non-cancer life stress, wishful thinking, maladaptive coping Social support</p>
Biomarkers and Health-Related Quality of Life in End-Stage Renal Disease: A Systematic Review (Spiegel et al., 2008)	Hct, nutritional markers (e.g. albumin, body-mass index)
Review article: epidemiology and quality of life in functional gastrointestinal disorders (Chang, 2004)	<p><i>Clinical</i> Symptom severity, symptoms periodicity, pain</p> <p><i>Psychosocial</i> Anxiety, stress, childhood adversity, poor sexual function because of irritable bowel syndrome (IBS), lack of social support, poor coping</p> <p><i>Sociodemographic</i> Age</p>
Disability and quality of life in headache: where we are now and where we are heading? (D'Amico et al., 2013)	Various treatments, such as migraine symptomatic and prophylactic medication and surgery

4.3 Proposed factors for inclusion in a biopsychosocial approach to HRQOL in MO

While acknowledging the significant contribution of purely biological studies to our understanding of headache's impact on daily life, Nicholson, Houle, Rhudy, Norton, and Forest (2007) explain that biology alone is not able "to account for all aspects of headache and disability" (p. 413) and that also investigating psychosocial factors could augment our research and therefore also improve patient treatment. The authors argue that a biopsychosocial approach to the study of headache would best serve such goals. They go on to explain that the central circuitry involved in cognition and affect overlap with mechanisms that modify pain. While Nicholson et al. use serotonin as their example, this study focuses on the glutamate as it plays roles in pain (Hashimoto et al., 2007; Mathew, 2001; Sarchielli, Di Filippo, et al., 2007) and has potential as a biomarker for MO (Anttila et al., 2010; Freilinger et al., 2013). Combined with the evidence that biomarkers do have a role to play in determining HRQOL, including glutamate in this research was seen as a justifiable step.

In examining which psychosocial variables show promise for migraine HRQOL, temperament stood out as a variable of great interest. For Chess and Thomas (1996) temperament is "one of the basic aspects of the psychological mechanism of behavioural functioning" (p. 3). Temperament is frequently associated with the development of psychopathology (De Pauw & Mervielde, 2010; Nigg, 2006). Boz et al. (2004) point out that some studies have shown that migraine is related to HA and P temperaments (Mongini, Fassino, et al., 2005). In turn, temperament influences which coping strategies one uses (De Boo & Spiering, 2010; Rueda & Rothbart, 2009) and how one perceives and uses social support (Kitamura et al., 1999).

4.4 Conclusion of Chapter 4

The HRQOL of migraine patients is generally poor. Explaining or predicting this HRQOL has been a challenge. In order to understand HRQOL in MO, an examination of potential determinants is necessary, but which of the many possible determinants to examine is linked to how one conceptualises HRQOL. In biopsychosocial terms, this means that looking at the various spheres of a patient's life can help us understand HRQOL.

Temperament represents one's automatic emotional response and has a strong biological basis at the neurotransmitter level. Temperament has been associated with coping, pain perception, lifestyle habits and perceived social support in various conditions. It is therefore posited that the impact of MO on HRQOL is influenced by types of coping mechanisms the individual employs as well as levels of perceived social support – underpinned by temperament, which in turn is linked to neurotransmission.

Chapter 5: Methodology

This chapter begins with a recap of the aims and research questions that were outlined in Chapter 1. The focus then moves to locating the research within its methodological framework, which includes a critical discussion of how the research questions informed the epistemological and ontological assumptions underpinning the study. The chapter ends with a description of the sampling and recruitment strategies for the research.

5.1 The research aims and questions

The purpose of this research was the exploration of HRQOL in MO. Exploratory research is mainly concerned with generating concepts and exposing patterns of relationships that can be tested further (Cargan, 2007; Louis Cohen, Manion, & Morrison, 2005; Stebbins, 2001).

The research began with three aims linked to specific research questions. Owing to the exploratory nature of the study, no hypotheses were posited. The first aim was to compare HRQOL amongst MO sufferers and non-migraineurs (NM). The research question formulated for this aim was: In what way does the HRQOL of MO sufferers differ from that of NM? The second aim of the research was to explore the association between temperament and pain coping in MO; the research question was posed as: What is the relationship between the harm avoidance (HA) temperament category and catastrophizing in MO? The third aim of the study was to examine how neurotransmission, temperament, pain coping, perceived social support and lifestyle factors contribute to the HRQOL experienced in MO. The research question was posed: To what extents do temperament, neurotransmission profile, coping strategy and perceived social support explain the variance in HRQOL in MO?

5.2 Research paradigm

Living systems are complex and they evolve. To believe this is perhaps also to believe that the quest to discover a single truth about such systems is too ambitious. Even within once strictly positivist fields such as neuroscience, shifts have occurred toward investigating subjective experience (Koyama, McHaffie, Laurienti, & Coghill, 2005; Solms & Turnbull, 2002); opening dialogue with postmodernist theory (Cage, 2013); and acknowledging the role of power in what researchers choose to study, how our values and cultures impact how one interprets what is found and how this impacts on society (Farah, 2005; Roskies, 2002).

All of this reflects the shift from staunch positivism to the postpositivism that guides this research. While a full discussion of postpositivism is beyond the scope of this chapter, three key points of postpositivism as they apply to this research require explication, namely: The question of realism; the objectivity of the researcher; and what constitutes knowledge / application of the scientific method.

5.2.1 Epistemology.

The study of pain processes is superficially divided into investigations of nociception (how pain is processed) and clinical pain (such as chronic or episodic pain). Whereas nociception research is largely conducted using objective measures such as quantification of autonomic and central responses (e.g. Gybels, Handwerker, & Van Hees, 1979; Hartley & Slater, 2014; Sikandar, Ronga, Iannetti, & Dickenson, 2013), the study of clinical pain relies heavily on subjective patient reporting (e.g. Hjermstad et al., 2011; Patel, Guralnik, Dansie, & Turk, 2013)

For pure positivists, subjective reporting becomes a confounding variable (Hitt, McMillen, Thornton-Neaves, Koch, & Cosby, 2007; Lasch et al., 2002). Added to this research complexity are issues of the multi-dimensionality of pain and comorbidities with diseases such as depression (Mao, 2009). As a solution to some of these challenges, Mao

(cited in De Benedittis et al., 1990, p. 1002) suggests that pain research requires “coordinated bidirectional research approaches between bedside and bench in order to bridge the gap between pain research and clinical pain management”. This implies that the study of multi-faceted concepts such as MO and HRQOL can benefit from a less reductionist approach than is supported by the boundaries of traditionally delineated academic disciplines.

In keeping with Mao’s premise, this thesis combines genomic research with physiological and psychological measures to guide the exploration of HRQOL in MO. The combination of genotyping and phenotyping data was viewed as useful in bridging the gap between bench and bedside (Luciano et al., 2011). Working across the genetic, molecular and psychological levels is labour-intensive, but allowed a look beyond nociception mechanisms in order to include broader aspects of pain mediation such as subjective responses and psychological traits and relationships (Mao, 2009).

The inter-disciplinary approach also allowed me to explore many possibly interconnected aspects at once (Dyer, 2003; Phoenix et al., 2013). By drawing from the disciplines of psychology, physiology and genetics, the researcher was able to enter a respectful line of inquiry in which the subject is seen as a complex being and not solely a collection of symptoms. However, the researcher was aware that marrying the knowledge and methods from social and natural sciences is complicated by the seemingly irreconcilable paradigmatic approaches of the disciplines. Phoenix et al. (2013) caution against automatically framing inter-disciplinary research within a single paradigm for the sake of avoiding this problem of these clashing paradigms. The authors go on to make a case for inter-paradigmatic research in which antitheses are crystallized to create approaches that traverse paradigms.

For postpositivists, what constitutes knowledge depends on the purpose of the research, for example policy creation or social change (Phoenix et al., 2013; Ryan, 2006). In acknowledging this, postpositivists also accept that the researcher has an agenda that is used

to determine the type of data that would best fit and the way in which it should be gathered. Consequently, neither the choice of subject matter, nor the choice of method is objectively derived. It is important to point out that the pragmatism of the biopsychosocial approach (Lewis, 2008), which is discussed in Chapter 3 links well with the postpositivist principle of choosing the best fit between the desired data form and the means of gathering the data.

The choice to study migraine grew from the observation of a lack of data in South Africa and the experience in practice that pain is sorely misunderstood by health care providers, families and sufferers and often misattributed to malingering or lack of commitment. Therefore, the study was undertaken in order to generate knowledge that will be useful in pain management programmes.

The choice to explore migraine from biological and psychosocial perspectives is a product of the researcher's belief about the reciprocity inherent in relationships between social milieu, psychological well-being and physiological functioning. The use of a biologically based concept (temperament) as a starting point in this study pushed a quantitative agenda. The quantitative method was therefore utilized, with cross-sectional research design and stages of descriptive and correlational process in an attempt to yield warranted assertions (Boyles, 2006; Floden, 2009; Wellman, n.d.).

5.2.2 Ontology.

The basis of postpositivism is critical realism, which combines a belief in the existence of some objective reality with a belief that any data is open to interpretation and therefore value-laden (Fischer, 1998; Ryan, 2006). As researchers, our presence shapes and colours the inquiry and we accept this ontological compromise (Fox, 2008).

The researcher is clear that the biopsychosocial standpoint from which the researcher is punctuated allows for the theoretical representation of only *a* reality. The ontological assumption of postpositivism is that objective reality is a possibility, though not a foregone

conclusion in any study. The researcher therefore aimed to represent the complexity of the matter as best as she could, while acknowledging that her subjectivity or the context in which the investigation occurs has a profound impact on, for example, which concepts are included for investigation (McKelvey, 2001; Parry, Gnich, & Platt, 2001). In this study, the choice of temperament, neurotransmission profile, coping and social support as the key variables in determining HRQOL in MO can be seen as subjective, although the choice was based on evidence from literature.

Ryan (2006) frames the postpositivist stance towards development vs. testing of theories as adopting a learning - rather than testing - role in research. The essence of a learning stance is in acknowledging that findings may lead to further questions. The researcher has proposed that HRQOL can be understood and predicted using a set of measurable biological, psychological and social parameters. Although the researcher tried to reflect some of the complexity of HRQOL in the model, she is not uncomfortable with the notion that there is no single theory that cannot be challenged with new data. For this reason the model is considered to be *a* reality and not *the* reality for MO sufferers.

5.2.3 Design.

This postpositivist paradigm together with the goal of quantifying various factors in this study led easily to a quantitative approach (Creswell, 2003). The first phase of the study made use of a cross-sectional survey design. In line with the general purpose of surveys, this survey was designed to gain information from a large sample of the population (Fowler, 2009). Some of this information was then used to select cases and NM participants for the second phase of the study. The second phase made use of retrospective, cross sectional design. No interventions were implemented.

This study began with a survey of the occurrence of migraine (MO and MA) in Gauteng, South Africa (phase 1). This phase was quantitative and descriptive. The data from this phase was used to answer the first two research questions.

From the initial sample ($N = 341$), 43 MO and 23 NM participants were chosen (Phase 2). This phase was comparative and correlational. Data from these 66 participants was used to examine the third research question. The NM and MO participants were compared in terms of glutamate levels, clinical laboratory results, transporter expression, demographic and psychosocial variables. Correlations were investigated between key variables before regression analysis.

5.2.4 Sampling and recruitment.

Phase 1 made use of convenience sampling. The choice of the Gauteng province was based on the fact that it is the most densely populated province in South Africa. Nearly a quarter of the country (12.9 million people or 24%) reside in this province (Statistics South Africa, 2014). Questionnaires were distributed electronically throughout the province. The planning of the sampling for this phase of the research was based on the original plan to conduct structural equation modelling. The recommended minimum number for such analysis is 200 (Kline, 2011).

For Phase 2, a sub-sample of the participants in Phase 1 was selected. MO and NM that had indicated willingness to donate blood for analysis were invited to participate. These participants were requested to supply blood samples for genetic and clinical laboratory testing.

Participants were recruited using a mixture of media and field work approaches between 2014 and 2015. The research was advertised in a local health magazine (Melomend Health); on the free international research advertising site, Call for Participants; using Google Adwords over 30 days (March / April 2015). The study was also profiled on the UNISA

campus radio show, UNISA Radio, for four weeks (October / November 2014) as part of a broader conversation on migraine. Four postgraduate students were recruited to assist with marketing the study. One was involved in researching a different aspect of MO at Master's level and the other three were students at another South African university. The latter were required to become involved in an aspect of research as part of a credit-bearing course at their institution. These students found the researcher via the study's Facebook page and contacted the researcher for an opportunity to work on the advertising. These students handed out pamphlets and collected e-mail addresses of people that wanted to have the study link sent to them.

In addition, two high schools, three higher education institutions, five allied medical societies and two corporates agreed to disseminate the survey link to their members or employees. No permission was granted to name these sites.

Furthermore, the study link and approximately 6 000 flyers were distributed through restaurants, cafés and social networks in Pretoria. A Twitter campaign ran for four months (December 2014 to March 2015) and a Facebook page was created to market the study and inform the public about migraine symptoms, advances in management and means of managing the impact of the headaches on daily life (May 2014 to May 2015).

5.2.5 Self-report data.

As mentioned in Chapter 2, there are some debates around the diagnosis of migraine cases using self-reporting. The ideal would be that such data is screened by a specialist physician and that laboratory investigations are included to rule out confounding variables. Nevertheless, self-reporting of signs and symptoms remains an acceptable and widely-used – not to mention practical - means of collecting headache data (Schürks et al., 2009).

The use of psychometric scales that rely on self-reporting has been criticised because the method relies on the assumption that participants have the necessary insight into their

psychological processes to answer reliably (Malt & Ursin, 2003). It does become more difficult to embrace such an assumption when seeing the pattern of, inter alia, catastrophizing and depression in migraine patients (Boz et al., 2004; Mongini et al., 2003; Mongini, Fassino, et al., 2005). Despite this, self-reporting does remain an acceptable form of data collection.

5.2.6 Ethical considerations.

The ethical considerations for this research were myriad. Not only did the researcher have to consider the questions of best practice in relation to the collection of psychological data, but it was also necessary to engage with questions about how best to anonymize data without losing the ability to link psychological and laboratory results, how best to explain the laboratory procedures to participants, the reporting of incidental findings and the storage / destruction of genetic material.

The relevant guidelines were considered to be: Unisa's Research Policy (University of South Africa, 2006), the National Institutes for Health (NIH, 2012) and the 1000 Genomes Project (1000 Genomes, 2012) and H3 Africa (H3Africa Working Group, 2013) guidelines on genomic research. The researcher followed the requirements of Unisa for ethics clearance. A copy of the informed consent brochure can be found in Appendix A.

Using these guidelines, the researcher built in three levels of consent for participants. The first level pertained to consent to participate in the survey and the second to be contacted to potentially supply blood samples. The third level was consent to supply blood specimens. The principles of the phlebotomy and the laboratory methods were included in the informed consent along with the guarantee that all unused specimens would be destroyed post-research. All participants were informed of the potential benefits of having their routine laboratory results shared with their healthcare practitioners and were encouraged to supply contact details for these practitioners. All results were then sent in a standardised report format to these practitioners.

5.3 Conclusion of Chapter 5

There are three research questions posed in this thesis: (i) In what way does the HRQOL of MO sufferers differ from HRQOL of those without MO? (ii) What is the relationship between the harm avoidance (HA) temperament category and catastrophizing in MO? And (iii) To what extents do temperament, neurotransmission profile, coping strategy and perceived social support explain the variance in HRQOL in MO? As this was an exploratory study, no hypotheses were associated with the questions.

These research questions were investigated from a postpositivist perspective, which acknowledges the links between neurotransmission, temperament, coping and social support determined within a biopsychosocial framework are only one version of reality for MO sufferers.

The pragmatism of the biopsychosocial approach and the postpositivist assertion that the nature of the data and its measurement have a good fit to one another and allowed the thesis to be conducted as interdisciplinary research that drew on the disciplines of psychology, physiology and genetics. Data were collected from adult residents of the Gauteng Province in South Africa. Participants were recruited using a number of social media and platforms and word of mouth. The data were analysed used quantitative methods to describe HRQOL and compare outcomes between MO sufferers and NM and explore the relationships between glutamate levels, clinical laboratory results, transporter expression, demographic and psychosocial variables

Chapter 6: Materials and Methods

This chapter describes the methods and materials for each of the two phases of the research. The measures are discussed in terms of what they are employed to determine, their scoring and reliability. The laboratory measures are described and, where relevant, their validation explained. Thereafter follow descriptions of the data analysis, a discussion of the ethical considerations in the research and the steps taken to ensure reliability and validity. Finally, the funding source and role players are described.

6.1 Materials and methods: Phase 1

Phase 1 consisted of a series of questionnaires that were administered via an online survey tool, Qualtrics. All participants were required to complete a biographical questionnaire that consisted of nine items about sociodemographic information, such as age, sex, highest level of education and ethnic origin. A further four questions were posed on personal health history, alcohol consumption and smoking.

All participants were also requested to complete the Short-Form 6 (SF-6D), Tridimensional Personality Questionnaire (TPQ), and Social Support Questionnaire (SSQ6). The question “How often do you experience headaches in a month?” was employed to screen out participants that do not suffer from any headaches: Individuals that answered “Never” were not required to complete any further headache questions. Participants that chose any other option (“Less than once a month”, “Once a month”, “2-3 times a month”, “Once a week”, “2-3 times a week”, “4-6 times a week”, “Daily” or “More than once a day, every day”) were required to complete the Pain Catastrophizing Scale (PCS) and items to provide more information on the characteristics of the headaches suffered (the duration of the headache, severity of the pain, its location, triggers and treatments). The headache items were derived using information in the literature and various headache reporting questionnaires used in

clinical settings (Breslau & Davis, 1993a; Headache Classification Committee of the International Headache Society, 2005b; Sabo & Maddox, 2009).

In order to understand the medication use pattern in headache sufferers, three items about medication (over-)use (“Do you find yourself thinking about when next you will be able to take some headache medication, even if you do not have a headache?”, “Do you feel that the need for taking the medication is too strong to control even when you do not have a headache?” and “Do you find it difficult to cope without the medication, even if you are not having a headache?”) were included. These items were adapted from the Leeds Dependence Questionnaire and scored on a four-point Likert-type scale (0 = Never, 3 = Nearly always). The Leeds Dependence Questionnaire is a 10-item self-report questionnaire developed as part of a treatment evaluation package for substance dependence (Raistrick et al., 1994).

6.1.1 Short Form 6 (SF-6D).

The SF-6D is a 10-item measure of general HRQOL. The scale is a significantly shortened version of the SF-36, which contained 36 items (Brazier, Roberts, & Deverill, 2002).

The SF-36 has been used in a number of headache studies (Aydemir, et al., 2011; Brown et al., 2008; Wang et al., 2001). The SF-36 measure is composed of eight subscales, namely: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems and mental health (MH). These eight subscales yield a physical and a mental health component score (Montazeri et al., 2011).

The SF-6D, on the other hand, has only six dimensions: physical functioning, role participation, social functioning, bodily pain, mental health and vitality (Optum, n.d.). An index rating was generated to illustrate the individual’s health state from 0.0 (worst health state) to 1.0 (best health state) (Hanmer, 2006; Optum, n.d.). This index and the scores for the

six dimensions were calculated using an algorithm developed by the University of Sheffield (University of Sheffield, n.d.).

The SF-6D has been used across a number of studies (Bozzani, Alavi, Jofre-Bonet, & Kuper, 2012; Keating, Peeters, Swinburn, Magliano, & Moodie, 2012; Shiroiwa et al., 2015). However, the measure does not yet appear to have been used in migraine studies. A number of population norms have also been developed for a number of countries, including Australia, Brazil and Japan (Shiroiwa et al., 2015; University of Sheffield, n.d.), but not for South Africa.

SF-6D performance in this thesis

Although the SF-6D provides a number of scores, the index score that is relatable to the SF-12 is referred to as the SF-12 index score or the SF-6D preference-based measure of health. In this thesis it is referred to either as the HRQOL or as the SF-12 index score, which gives the overall health-related quality of life index score from 0 to 1.

The central tendencies and distributions for the SF-6D index in this study are shown in Table 6.1. The data are non-normally distributed, with skewness of ranging from -.59 to .34 ($SE = .13$) and kurtosis varying from an insignificant -.01 to -.69 ($SE = .26$).

Table 6-1: Central tendency and distribution for the SF-6D-4 in the current study ($N = 341$)

SF12index (represents HRQOL)	Minimum	Maximum	Mean	SD	Skewness		Kurtosis	
					Statistic	SE	Statistic	SE
	.39	1.00	.73	.13	-.179	.132	-.83	.26

SF-6D has been found to be reliable in estimating HRQOL in systemic sclerosis (Khanna et al., 2007) with good test-retest reliability ($ICC = 0.82$ [95% CI: 0.76, 0.87]), though some floor effects are noted for the poorest health states (Brazier et al., 2002) The

Cronbach α score was calculated using the transformed and not the raw scores for the SF-6D. The score was .78, which is higher than the .7 limit for acceptability (Lowenthal, 2001). It is therefore adequate.

6.1.2 Tridimensional Personality Questionnaire (TPQ).

The TPQ is based on Cloninger's Psychobiological Theory of Personality and consists of 98 items rated as either true or false by the respondent (Stewart, Ebmeier, & Deary, 2004). The TPQ originally distinguished three temperament dimensions – Harm Avoidance (HA), Novelty Seeking (NS) and Reward Dependence (RD). Later, it was found that some items did not measure RD, but rather a fourth dimension called persistence (P) (Verweij et al., 2010).

The TPQ cannot be marked by the researcher and has to be scored through Anthropedia, an organisation that markets and sells the test. The algorithm for scoring the test is not publicly available. The results returned indicated the totals for the three original dimensions. Each scale has four subscales labelled 1 to 4. However, the subscale RD2 is now regarded as the measure of P. The scales and subscales as well as their descriptions are shown in Table 6-2 (adapted from Celikel et al., 2009; Hansenne et al., 1999; Mardaga & Hansenne, 2007; Sovio et al., 2007; Verweij et al., 2010).

Table 6-2: Scales, subscales and descriptions of the Tridimensional Personality

Questionnaire (TPQ)

<i>Scale and description</i>	<i>Subscale and description</i>
Novelty Seeking (NS): Level of activation of exploratory activity (33 items)	NS1: Exploratory excitability
	NS2: Impulsiveness
	NS3: Extravagance
	NS4: Disorderliness
Harm Avoidance (HA): The efficiency of the behavioural inhibition system (34 items)	HA1: Anticipatory worry
	HA2: Fear of uncertainty
	HA3: Shyness with strangers
	HA4: Fatigability
Reward Dependence (RD): Maintenance of rewarded behaviour (22 items)	RD1: Sentimentality
	RD3: Attachment
	RD4: Dependence
Persistence (P): Maintenance of behaviour as resistance to frustration (9 items)	RD2: Persistence

TPQ performance in this thesis

The central tendencies and distributions for the TPQ dimensions in this study are shown in Table 6.3. The data are non-normally distributed, with skewness of ranging from -.59 to .34 ($SE = .13$) and kurtosis varying from an insignificant -.01 to -.69 ($SE = .26$).

Table 6-3: Central tendency and distribution for the TPQ in the current study

TPQ dimension	Minimum	Maximum	M	SD	Skewness		Kurtosis	
					Statistic	SE	Statistic	SE
NS	2.00	30.00	14.56	5.54	0.25	0.13	-0.30	0.26
HA	0.00	34.00	14.82	7.60	0.34	0.13	-0.69	0.26
P (RD2)	0.00	9.00	5.82	1.91	-0.59	0.13	-0.01	0.26
RD	2.00	28.00	17.43	4.64	-0.19	0.13	-0.39	0.26

The test has generally demonstrated adequate psychometric properties, such as internal consistency levels that range from 0.55 to 0.89 (Sher, Wood, Crews, & Vandiver, 1995). The test and Cloninger's theory continue to enjoy wide use in both clinical and non-clinical populations. The Cronbach α scores for the scales of the TPQ were calculated by Anthropedia as: NS $\alpha = .78$; HA $\alpha = .90$; RD $\alpha = .72$ and P $\alpha = .56$. All the scales are adequately reliable, except for P.

6.1.3 Social Support Questionnaire 6 (SSQ6).

The SSQ6 is a six-item questionnaire measuring perceived social support (Sarason, Sarason, Shearin, & Pierce, 1987). Each item has two parts: The first part asks the subject to list the people that can be relied on for support in a specific situation; the second part asks the subject to rate his / her satisfaction with the perceived support on a scale of one to six (1 = Very satisfied, 6 = Very dissatisfied). Each item is scored according to the number of people listed as sources of support. Two scores are computed, the first by dividing the sum of people named (a maximum of nine people may be listed per item) by the number of items and the second by dividing the sum of satisfaction scores by the number of items (Callaghan, 1998; Monteiro, 2011). The focus of this study rested on the amount of perceived support, so only the first score was computed.

SSQ performance in this thesis

The objective of this study was to study social support only in terms of the perception of how many people are available to lend support. In order to obtain a score for this aspect of

social support the formula from the SSQ6 scoring instructions was utilised: $SSQ_{TotalNumber} = \Sigma (\text{Items } 1a, 2a, 3a, 4a, 5a, 6a) / 6$. The maximum possible score on this index is six and the minimum is zero. The distribution and central tendency for the number of supporters subscale is shown in Table 6.4. The data are non-normally distributed, with skewness of .43 ($SE = .13$) and kurtosis of -.60 ($SE = .26$).

Table 6-4 :Central tendency and distribution for the SSQ6 items related to the amount of social support in the current study ($N = 340$)

SSQ6	Minimum	Maximum	M	SD	Skewness		Kurtosis	
					Statistic	SE	Statistic	SE
	0.50	7.83	4.03	1.75	0.43	0.13	-0.60	0.26

The instrument has shown high reliability coefficients for both subscales at 0.97 and 0.94, respectively (Callaghan, 1998). The Cronbach α for the six items was .83, which indicates good internal consistency.

6.1.4 Pain Catastrophizing Scale (PCS).

The PCS consists of 13 items that evaluate the negative cognitions and emotions related to pain (Sullivan, Rouse, & Bishop, 1997). Items are scored on a 5-point scale (0 = Not at all, 4 = All the time). The global score indicates the level of catastrophizing, while the three subscales measure rumination, magnification and helplessness (Sullivan, 2009) The total PCS score is derived by summing the responses to all 13 items. Scores range from 0 to 52, with higher scores indicating greater use of catastrophizing for coping with pain. The subscale scores are derived as follows:

- (i) Rumination = Σ (Items 8, 9, 10, 11)
- (ii) Magnification = Σ (Items 6, 7, 13)

(iii) Helplessness = Σ (Items 1, 2, 3, 4, 5, 12)

A shorter version of the PCS was developed by Bot et al. (2014). The revised scale makes use of items 3, 6, 9 and 11 to yield an overall catastrophizing score. It has been found to have good internal consistency ($\alpha = .86$) and correlated strongly with the 13-item PCS ($r = .96$). Further evaluation of this four-item PCS (referred to as the PCS-4) was conducted in a group of chronic musculoskeletal pain patients ($N = 280$). Again, the PCS-4 showed significantly strong correlation with the original ($r = .93$) and high internal consistency ($\alpha = .81$). This shorter version was employed in the current study.

PCS-4 performance in this thesis

The central tendency and distribution for the PCS-4 in this study is shown in Table 6.1. The data are non-normally distributed, with skewness of .99 ($SE = .14$) slight kurtosis of .09 ($SE = .28$).

Table 6-5: Central tendency and distribution for the PCS-4 in the current study ($N=311$)

PCS-4	Minimum	Maximum	M	SD	Skewness		Kurtosis	
					Statistic	SE	Statistic	SE
	0	16.00	4.26	4.27	0.99	0.14	0.09	0.28

The test has been used extensively in pain studies and translated into various languages (Cho, Kim, & Lee, 2012; Fernandes, Storheim, Lochting, & Grotle, 2012; Morris, Grimmer-Somers, Louw, & Sullivan, 2012). The test has shown acceptable reliability for use in clinical and non-clinical populations (Osman et al., 1997). The PCS has acceptable internal consistency: total PCS $\alpha = .87$, Rumination $\alpha = .87$, Magnification $\alpha = .66$, and Helplessness $\alpha = .78$ (Sullivan, 2009). The Cronbach α for the four items was .89. This indicates good internal consistency.

6.2 Data analysis plan for Phase 1

Questionnaires were completed on Qualtrics, which is an electronic survey site (www.qualtrics.com). Each participant was randomly assigned a unique participant identification number by the Qualtrics software. All data were downloaded in .csv format, cleaned and then exported to SPSS.

The TPQ copyrighted limits scoring to the sole distributor, Anthropedia. All information was removed from the data set, except the unique identifier and the TPQ items. The file was sent to Anthropedia. The scored data were then returned via e-mail.

The SF-6D data were scored on the software provided by the University of Sheffield. The algorithm provided could be directly applied to the SPSS data.

The attrition rate was calculated using the number of incomplete questionnaires as a percentage of all questionnaires started. Diagnosis of MO was established using the ICHD-II criteria. Interval data were described using the mean or median and standard deviation, while categorical variables were described in frequencies and percentages.

During analysis of the phase 1 data, four groups emerged from preliminary analysis: Those that had never experienced a headache (Group 1); participants that have experienced headaches, but not MO (Group 2); those with possible MO (Group 3) and those with MO (Group 4). Between-group differences for ordinal and continuous data were calculated using the Kruskal-Wallis Test. Although analysis of variance (ANOVA) is popularly used for such comparison, the sample did not meet the assumption of normality required (Field, 2013). In addition, the group sizes differed considerably and this can have a significant effect on ANOVA calculation (Bliese & Halverson, 1998). Between-group differences for categorical data were calculated using Chi-square or Fisher's Exact Test.

Correlations were calculated using Spearman's rho. The correlations were also executed controlling for variables that showed significant differences in the group

comparisons. Effect sizes for correlations were classified as trivial (<.1), small to medium (.1-.3), medium to large (.5-.8) and large to very large (>.8) (Cohen, 1992).

The data were then explored for suitability to conduct regression analyses. The specific criteria and steps for suitability are discussed in detail in Chapter 7. These criteria were met, allowing for the use of hierarchical regression. Mediator and moderator effects were investigated using the PROCESS method (Hayes, 2013).

6.3 Materials and methods: Phase 2

Participants consenting to providing blood for Phase 2 underwent a set of laboratory tests. These laboratory tests were used to help understand the pattern of dysfunction that may occur in MO and to guide the sample selection. Participants were requested to be headache-free for seven days before providing samples.

Samples were collected by registered phlebotomists at the Ampath Laboratory of the subject's choice (after 10-hour fast). The fasting glucose, clotting and lipid profile tests were carried out by Ampath Laboratories. These three sets of results were used to describe the overall health profiles of the participants in Phase 2. The researcher conducted the glutamate ELISA and qPCR determinations at the University of Pretoria.

6.3.1 Fasting glucose.

This test is used to detect abnormal blood sugar levels such as those seen in diabetes. Blood (3ml) was collected in a heparinised tube, then centrifuged and separated within 45 minutes of collection. The glucose concentration was quantified using a hexokinase-mediated reaction via the Roche/Hitachi Modular P Chemistry analyzer (University of Minnesota Medical Center, Fairview Collaborative Studies Clinical Laboratory Minneapolis, n.d.). The reference range used by Ampath for fasting glucose is 3.9–6.0 mmol/l.

6.3.2 Clotting.

The measure of the efficiency of the intrinsic clotting pathway is called activated partial prothrombin time ratio (aPTT ratio). Ampath phlebotomists collected 3.5ml of blood in a citrate tube and an activator was added before starting the clotting process (Practical Haemostasis.com, 2016). The ratio is calculated using the absolute aPTT by the midpoint of the reference range (University College London Hospitals, 2012) and should ideally be between 0.8 and 1.2.

6.3.3 Lipid profile.

Total cholesterol and triglyceride levels were measured by Ampath. Blood (4ml) was collected in Vacutainer blood collection tubes and left to stand for 45 minutes to allow complete clotting of the sample. The sample was then centrifuged at 1,500 x g for 30 minutes at 4°C. Cholesterol and Triglycerides/GPO reagents were used to digest the cholesterol for analysis on a Hitachi 704 Analyzer (Lipid Laboratory Johns Hopkins, 2003).

The reference range utilised by the Ampath Laboratory are as follows:

- (i) Total cholesterol: 2.8-4.9 mmol/l
- (ii) Triglycerides: 0.4-1.6 mmol/l
- (iii) High density lipoproteins (HDL):
- (iv) Low density lipoproteins (LDL): 1.2-1.9 mmol/l
- (v) Non-HDL Cholesterol: 0.9-3.7 mmol/l

6.3.4 Enzyme-linked Immunosorbent Assay.

Enzyme-linked Immunosorbent Assay (ELISA) is an umbrella term for a number of immunoassays that involve the use of a reagent immobilised on a solid phase together with an enzyme that acts as a signal generator (Butler, 2008). The ELISA technique was developed by Engvall and Perlman in 1971 (Charan & Gautam, 1984; Engvall & Perlmann, 1971). ELISA is a widely used laboratory technique for quantifying the concentration of an analyte (AbDSerotec, 2015; Lequin, 2005), based on the principles of antibody immunological reactions. There are a number of types of ELISA depending on, for example, whether the

antibody or the antigen is immobilized, whether the assay is competitive or not and whether the immune response to the analyte is measured directly or indirectly. The technique is distinguished from other assays by its use of antibody-antigen binding in detecting the analyte (SeraCare Life Sciences, 2013). The enzyme acts to report that the specific antibody-antigen reaction has occurred and can also be used to quantify the extent of the reaction (Butler, 2008).

6.3.5 Glutamate ELISA.

Glutamate concentration was quantified in this research using Abnova's glutamate ELISA kit (catalogue number KA1909). The kit is used for quantifying L-glutamate in urine, plasma and serum. This is a competitive assay, meaning that the reference and sample analytes compete for binding to a limited number of antibody binding sites. Antigen is bound to a solid phase of the plate. Free antigen and antigen-antibody complexes are washed away after the reaction has reached equilibrium (Abnova, n.d.; SeraCare Life Sciences, 2013).

Blood (5mL) was collected in an EDTA tube, centrifuged at 3000rpm and transferred to 1.5ml Eppendorf tubes before storage at -20°C. Samples were stored for six months and were defrosted for an hour before use. Each subject's sample was tested at least in duplicate, although 19 were conducted in quadruplicate (for quality assurance). Statistical analysis was conducted using the mean concentrations of the replicates.

ELISA performance in this thesis.

The central tendency and distribution for the ELISA in this study is shown in Table 6.6. The data are non-normally distributed, with skewness of .1.557 ($SE = .295$) and kurtosis of 2.454 ($SE = .582$).

Table 6-6: Central tendency and distribution for the ELISA glutamate results in the current study ($n = 66$)

Glutamate serum ELISA ($\mu\text{g/ml}$)	<i>Minimum</i>	<i>Maximum</i>	<i>M</i>	<i>SD</i>	<i>Skewness</i>		<i>Kurtosis</i>	
					<i>Statistic</i>	<i>SE</i>	<i>Statistic</i>	<i>SE</i>
	4.9	84.830	24.718	17.007	1.557	.295	2.454	.582

Abnova's glutamate ELISA kit is reported to have less than .1% cross-reactivity with aspartate, glutamine, glycine, alanine and 5-aminovaleric acid.

Precision was investigated through calculating the intraplate coefficients of variation (%CV), which indicate how much the duplicates vary from one another. The samples were split over two plates. The %CV of each plate was calculated using equation $\text{SD of optical density} / \text{mean optical density} \times 100$ (Crowther, 2002).

The intraplate %CVs were 10% for both the first and second plates. This indicated that duplicate concentrations of glutamate for the same sample varied by 10% on this kit. Such variations mainly arise because of inadequate mixing of reagents or pipetting errors (Crowther, 2002). To improve the precision of the technique, all samples that exhibited more than 15% variance ($n = 19$) were re-run. The 15% cut-off is the recommended %CV for ELISA (Crowther, 2002). A pipetting error saw a single row receive twice the required Q-Buffer. The optical densities for those eight samples were excluded and the concentration was calculated only on the one reading. The CV for the third kit was improved at 7%. This was considered to be within normal experimental error limits for this type of assay. The concentration for a sample was calculated using the duplicate optical densities from the plate where the readings had the lowest %CV.

6.3.6 Transporter investigations.

EAAT2 expression was quantified via real time reverse transcription (RT^2) / quantitative polymerase chain reaction (qPCR) using Qiagen's qPCR Primer Assay. qPCR is

the process of amplifying DNA sequences exponentially and measuring the quantity of amplified product (Nolan, Hands, & Bustin, 2006; Pestana, Belak, Diallo, Crowther, & Viljoen, 2010). In traditional PCR amplification products are measured post-reaction using gel electrophoresis (Fraga, Meulia, & Fenster, 2008; Pestana, Belak, Diallo, Crowther, & Viljoen, 2010). However, qPCR involves continuous measurement of product throughout the reaction.

The qPCR has a number of steps and the work flow for this thesis is illustrated in Figure 6-1. qPCR involves the extraction of RNA, reverse transcription (RT) of RNA to cDNA and amplification of the cDNA (Nolan et al., 2006; Tichopad, Kitchen, Riedmaier, Becker, & Ståhlberg, 2009). The task is labour intensive and time consuming and has a number of check and balances at various stages.

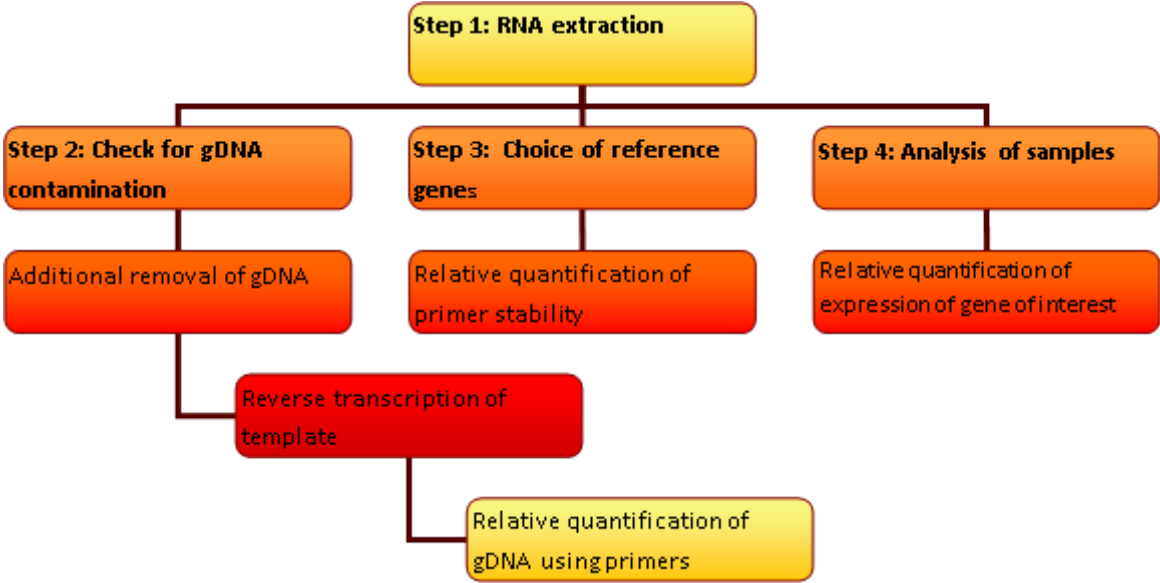


Figure 6-1: Steps in the qPCR workflow for this thesis

Specimen collection.

Samples of blood (2.5mL) were drawn by Ampath phlebotomists into Qiagen’s Preanalytix PAXgene Blood RNA Tubes. These tubes contain a patented agent for RNA

stabilization, which prevents RNase action and limits gene induction (Magee, 2011). Samples can remain stable for 3 days at 18 – 25°C, 5 days at 2 – 8°C and at least 50 months at -20°C. Samples were stored for six months at -20°C before use.

Isolation of RNA.

Qiagen's PAXgene Blood RNA Kit was used to prepare total RNA from the whole blood. The process for manual isolation of RNA was followed in this thesis (Preanalytix, 2015).

This process is column based. It involves the digestion of proteins by proteinase K before removal of cell debris on the shredder column. This is followed by several wash steps, before the elution of the RNA (Preanalytix, 2015).

Quality assurance.

The extracted total RNA was analysed using spectrophotometry on the NanoDrop ND-1000. Samples were evaluated on three criteria: (i) RNA concentration (determined by A260) had to be $\geq 200\text{ng}/\mu\text{l}$, (ii) A260:A280 values had to be ≥ 1.5 and (iii) A260:A230 had to be ≥ 1 .

Although these criteria are less stringent than those suggested by the manufacturer (Qiagen, 2015), the adjustments were a practical necessity because of low yield. The low yield is caused by challenges or errors in any stage of the extraction, storage challenges and protein contamination – it can be difficult to pinpoint (Kennedy, 2014). An additional step was undertaken to minimise the effect of low yield: The elution of RNA was conducted with 40 μL or supplied eluent, rather than 80 μL , in order to increase concentration. Of the 66 original samples, 26 (40%) met the criteria.

qPCR Assay.

Quantification of levels of EAAT2 expression was attempted in the remaining 26 samples. The cDNA synthesis was carried out using Qiagen's First Strand Kit and 200ng of

RNA extracted from the sample using dual hybridisation probes - Qiagen's SYBR Green - on Roche's LightCycler Nano. Qiagen's SYBR Green Mastermix is fluorescence based binding dye technology. The dye binds double-stranded DNA and the amount of cDNA is detected by the increase in fluorescence through the reaction.

Each reaction was performed in a final volume of 25 μ L (1 μ L cDNA diluted with 10.5 μ L of RNase-free water, 1 μ L Qiagen RT² qPCR primer assay and 12.5 μ L of Qiagen's RT² SYBR Green Master Mix). The amplification process was started with 10 minutes of activation at 95°C. This was followed by 55 cycles of 95°C for 15s and 60°C for 1 minute. All samples were run in duplicate and mean values were calculated. The efficiency of the process is reportedly greater than 90% (Qiagen, 2012). The quantification cycle, also sometimes known as the threshold cycle (C_t) was determined for the reference genes and the gene of interest (GOI) in each sample. The Livak method was utilized for data analysis. All non-detected C_t values were imputed using the model described by Mccall, McMurray, Land, and Almudevar (2014). The mean C_t was calculated for the genes. Livak's Method (Livak & Schmittgen, 2001) was used to calculate fold change: Mean values were calculated for the C_t values of gene of interest (SLC1A2) for the two groups. A mean C_t was calculated for the two reference genes together for the two groups. The first step was normalisation: The differences C_t in between the gene of interest and the reference genes (ΔC_t) was calculated as $\Delta C_t = \text{Mean}(C_t\text{GOI}) - \text{Mean}(C_t\text{Reference genes})$. The differences in C_t between MO and NM was calculated as $\Delta\Delta C_t = \text{Mean } \Delta C_t(\text{MO}) - \text{Mean } \Delta C_t(\text{NM})$. Finally, the fold change was calculated as $2^{(-\Delta\Delta C_t)}$. The central tendency analysis (Table 6-6) shows that the qPCR data is non-normally distributed.

Table 6-6: Central tendency and distribution for the qPCR normalized SCL1A2 and fold-change data in the current study ($n = 20$)

	<i>Minimum</i>	<i>Maximum</i>	<i>Mean</i>	<i>SD</i>	<i>Skewness</i>		<i>Kurtosis</i>	
					<i>Statistic</i>	<i>SE</i>	<i>Statistic</i>	<i>SE</i>
Normalized SCL1A2	0.015	5345.095	321.688	1194.132	4.339	0.512	19.091	0.992
Fold-change	-3.625	11.975	5.992	4.381	-0.703	0.512	0.341	0.992

Quality assurance.

There are a number of qPCR products available and, according to Nolan et al. (2006), no two methods produce the same results. The reasons for variation are myriad and some of these are described by Tichopad et al. (2009).

In an effort to diminish the effects of some errors sources across all these methods, standardised guidelines have been produced. The most notable guidelines are the Minimum Information for Publication of Quantitative Real-Time PCR Experiments or MiQE Guidelines (Bustin et al., 2009). The MiQE guidelines were followed in this thesis with regard to testing for genomic DNA (gDNA) contamination, biological replicates and the inclusion of endogenous controls or reference genes (sometimes called housekeeping genes) (Bustin et al., 2009).

GDNA contamination was evaluated using Qiagen’s gDNA Control primer assay. Each sample ($n = 26$) was run with Qiagen’s gDNA SYBR Green Mastermix and reverse transcriptase (+RT) and a no-reverse transcriptase no template control (-RT/NTC). A C_t value between 30 and 35 indicates that caution must be exercised when interpreting the results as gDNA contamination may have influenced the expression profiling. However, a C_t value above 35 suggests gDNA contamination that is too low to interfere with the reactions. All samples showed C_t values above 30. Any gDNA present is therefore unlikely to have affected the analysis.

Four reference genes were noted in the literature for SLC1A2. These were GAPDH (Miguel-Hidalgo et al., 2010), B2M (Vallejo-Illarramendi, Domercq, Pérez-Cerdá, Ravid, & Matute, 2006), RPL13A (Jacob et al., 2007) and ACTB (Martisova et al., 2012). The best performing reference genes were determined on nine samples. Ideally, the expression of reference genes should remain invariable (Qiagen, 2011b). The stability of a gene in expression is calculated using the log-transformed C_t (Spiegelaere et al., 2015). The worst performing reference gene was identified using the Microsoft Excel add-in, NormFinder (Molecular Diagnostic Laboratory, 2010). NormFinder is a free software tool that analysis gene expression stability, which is considered acceptable when <1.5 (Ling & Salvaterra, 2011). The most stable gene was RPL13A ($M = 1.042$) and the best combination of reference genes was RPL13A with GAPDH (combined $M = 1.395$). Subsequent runs were conducted only using these two reference genes. NormFinder has been used in numerous studies and has been found to be sufficiently reliable with small samples (Spiegelaere et al., 2015). Normalization of the data was therefore conducted with two reference genes. Table 6.7 shows the details of the genes used as the target and references.

A further check for gDNA was introduced during the reactions. A -RT control was run for every +RT reaction. A difference of six or more in the C_t value of the two (-RT - +RT) indicated that gDNA contamination did not affect the reaction (Qiagen, 2015). Reactions that showed differences less than six were excluded from analysis. Thus, the final sample was 20 for the qPCR analysis.

Table 6-7: Primers used for the qPCR

<i>Gene name</i>	<i>Primer assay catalogue number</i>	<i>Accession number</i>	<i>Length (bp)</i>	<i>Reference position (in RefSeq)</i>
Solute carrier family 1 (glial high affinity glutamate transporter), member 2 or excitatory amino acid transporter 2	PPH01440F	NM_004171.3	70	2213
Ribosomal protein L13a	PPH01020B	NM_012423.3	90	994
Glyceraldehyde-3-phosphate dehydrogenase (spermatogenic)	PPH14985F	NM_014364.4	100	686

6.4 Data analysis for Phase 2

Interval data were described using the mean, median and standard deviation, while categorical variables were described in frequencies and percentages. Between-group differences were calculated using the Mann-Whitney U Test or Student's t-test for interval variables, whereas χ^2 or Fischer's Exact Test was used for categorical variables. Given that the data are mainly non-normally distributed, Spearman's correlation coefficient was used instead of Pearson for interval variables as it is considered a more robust test for small samples (Field, 2000).

6.5 Ethical considerations

The guidelines supplied by the National Institutes for Health (NIH, 2012), the 1000 Genomes Project (1000 Genomes, 2012) and H3 Africa (H3Africa Working Group, 2013) were followed with regard to privacy, storage and analysis of genetic material. The Patient information and Informed consent leaflet reflects these guidelines. Participants were given the choice of providing their health practitioners' details for the routine blood test results.

The use of an online platform for the administration of tests posed potential challenges for maintaining confidentiality. For this reason, a platform with data security options was

used. The Qualtrics platform has various levels of data protection, including password protection and anonymizing of surveys. Only the primary researcher and the database administrator had access to this password. The database administrator signed a confidentiality agreement for the study.

The study was reviewed by the ethics committee of the Department of Psychology at Unisa. Clearance was granted for the study by that committee in 2013 (see Appendix B). The researcher was also granted permission to recruit staff and students at Unisa for the study. The latter required review by a separate committee and clearance was granted for this in 2014 (see Appendix B).

6.6 Reliability and validity

Several steps were taken to increase the reliability and validity of the process. The first step was to calculate power for the study in order to approximate the ideal sample size. Funding was secured to approach the ideal sample size. However, this sample size was not realised within the timeframe. Power calculations were carried out to determine effect sizes and these are reported in the results.

The second step was to ensure the reliability of the questionnaires chosen. For this reason questionnaires with a reported reliability close to 0.9 were chosen. Thirdly, the validity of the questionnaires was tested using the internal consistency method. These results are reported earlier in this chapter.

With regard to the blood tests, Ampath Laboratories is an accredited diagnostic laboratory. This laboratory conducted the cholesterol, glucose and clotting profiles. Although the ELISA and qPCR testing did not take place in an accredited laboratory, the measures were conducted under supervision and were conducted in duplicate. qPCR included reference genes.

6.7 Funding and roles

Funding for this research was provided by the National Research Foundation. Funding was approved through the Thuthuka PhD Track grant. UNISA waived all tuition fees, except registration fees as it does for all employees.

The collection of bloods and the standard laboratory assessments (fasting glucose, aPTT and lipid profile) were carried out by Ampath Laboratories, Pretoria, South Africa. The ELISA measures were carried out by the candidate at the Department of Physiology at the University of Pretoria under the guidance of Dr Alida Koorts and with assistance from Ms Jaqueline Harvey. Ms Harvey was a Master's student in the Department of Psychology, UNISA (under the researcher's supervision) at the time that the work was conducted.

The qPCR determinations were completed at the Department of Physiology at the University of Pretoria with training and support from Dr André Stander. Assistance was provided again by Ms Harvey and technical support by Ms Ting Hua Chang. Further theoretical training was provided by Dr Charles Wairuri from Whitehead Scientific, South Africa. The researcher conducted the statistical analyses in SPSS, with statistical support provided by Dr Mardé Booyse of the ARC.

6.8 Conclusion of Chapter 6

This thesis consisted of two data gathering phases. In phase 1 a survey was conducted to gather data on sociodemographics, migraine symptoms, temperament, social support and coping. Participants who indicated a willingness to donate blood specimens for analysis were invited to participate in phase 2. Ampath Laboratories collected the blood specimens and provided fasting glucose, total cholesterol and clotting analyses. The researcher conducted glutamate serum ELISA, qPCR and statistical analyses with the support of members of the Department of Physiology at the University of Pretoria, the ARC and Ms Jaqueline Harvey. The National Research Foundation provided the project funds.

Chapter 7: Results of phase 1

The data from phase 1 of the study are presented in this chapter. The phase 1 data is used to describe the occurrence of MO in Gauteng. HRQOL was examined and compared for NM and MO sufferers. This was followed by an examination of how the psychological data can help predict HRQOL.

7.1 Data collection and attrition for Phase 1

Survey data collection took place between May 2014 and July 2015. All adults living in the Gauteng province of South Africa were eligible to participate. Participants were recruited through various media and this process is discussed in detail in the methodology chapter.

Of the 723 people that started the questionnaire, 341 (47%) completed it. The questionnaire used piping to direct those that have experienced a headache to answer questions about their symptoms, while participants that stated that they had never experienced a headache ($n = 30$; 9%) did not have to answer these questions.

7.2 Exclusion from migraine without aura diagnosis and emergence of groups

Two participants reported that they had been diagnosed with a terminal illness. Six more reported having a degenerative nervous disorder. These eight participants were excluded from any migraine diagnosis. One participant reported weakness and 72 reported possible scintilla. All 73 participants described these as symptoms that occurred during headache and not as prodromal symptoms and therefore they were not classified as experiencing aura. No other possible signs of aura were reported.

As mentioned in the materials and methods (Chapter 6), four groups emerged during data analysis. These groups are: Those that had never experienced a headache (Group 1);

participants that have experienced headaches, but not MO (Group 2); those with possible MO (Group 3) and those with MO (Group 4). These groups were used in further analysis.

7.3 Headache characteristics

In order to gain insight into the headache characteristics for the sample, the occurrence of MO symptoms is described. Each criterion is described separately before the rates of MO and possible MO are presented. Table 7-1 shows the frequency with which the four migraine symptoms (ICHD-II criteria A to D) appears in the sample.

More than two-thirds of the sample experience headache on a monthly basis or more frequently ($n = 232$; 68%), with the rest ($n = 109$; 32%) never or seldom (less than once a month) experiencing a headache. More than a third of participants ($n = 128$; 38%) experienced headaches of more than 4 hours.

The mean severity of the pain associated with headaches in this sample ($n = 311$; 91%) was 46.72, $SD = 27.79$ on a 100-point scale. The moderate to severe classification is based on the VAS norms (45-100) (Jensen, Chen, & Brugger, 2003). There were 167 (49%) participants that described their average headache pain as moderate to severe.

It is worth noting that more than half of the sample experienced headaches of a pulsating nature ($n = 193$; 57%) or with nausea and / or vomiting or photophobia and phonophobia ($n = 176$; 52%). Few experienced aggravation of headache by or resulting in avoidance of routine physical activities ($n = 10$; 3%), unilateral location ($n = 29$; 9%).

Table 7-1: Frequencies (n, %) of migraine without aura symptoms (N = 341)

<i>Criteria</i>	<i>Frequency (n; %)</i>
A: At least five attacks	232; 68
B: Headache attacks lasting 4-72 hours	128; 38
C: Unilateral location	29; 9
Pulsating quality	193; 57
Moderate or severe pain intensity	167; 49
Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)	10; 3
D: nausea and / or vomiting or photophobia and / or phonophobia	176; 52

7.4 Migraine occurrence

MO and possible MO frequencies were calculated by identifying participants that met all four MO criteria (criteria A to D) or any combination of three of the criteria (ABC, ABD, ACD or ABD). All four criteria were met by 94 participants. The criteria for possible MO were met by an additional 62 participants, but two were excluded from diagnosis because they suffered from a degenerative nervous disorder. The occurrence of MO is therefore 28% and 18% for possible MO in this sample. Only three of the 94 participants meeting all four criteria for migraine reported having been diagnosed with a headache disorder.

7.5 Group comparisons

The four headache groups were compared on a number of variables. For ordinal or continuous variables such as age, medication overuse, frequency of alcohol intake or number of cigarettes smoked, groups were compared using the Kruskal-Wallis test. Chi-square tests were utilised when comparing categorical data. However, Fisher's Exact test was used to

investigate the difference between groups where an excessive number of cells had counts less than five and therefore a Chi-square was not suitable (Howel, 2013).

7.5.1 Demographics.

The mean age was calculated without missing values ($n = 323$) and was 36.64, $SD = 11.74$ years. The groups did not differ significantly regarding age distribution ($p = .748$).

The frequency distributions for a number of demographic variables are shown in Table 7-2. Only the highest frequencies of each category are shown. The results of the between-group comparisons are shown under p-values.

The majority of participants were female ($n = 268$; 79%), spoke English at home ($n = 177$; 52%), were employed ($n = 283$; 83%) and educated to the tertiary level ($n = 309$; 91%). The question on ancestry allowed for multiple responses for each individual. Most participants identified themselves as having European heritage ($n = 251$; 62%), while 98 (29%) identified with African heritage and 33 (10%) with Asian heritage.

There were no significant differences between groups [never experienced a headache (Group 1); participants that have experienced headaches, but not MO (Group 2); those with possible MO (Group 3) and those with MO (Group 4)] on highest level of education attained, employment category or ancestry. However, the groups differed significantly regarding the distribution of home language ($p = .035$) and sex ($p = .001$).

Table 7-2: Frequencies (*n*, % of group) of demographic information and comparisons across groups

<i>Variable</i>		<i>Total sample</i>		<i>Group 1</i>		<i>Group 2</i>		<i>Group 3</i>		<i>Group 4</i>		<i>p</i>
		<i>(N = 341)</i>		<i>(n = 44)</i>		<i>(n = 143)</i>		<i>(n = 60)</i>		<i>(n = 94)</i>		
				<i>Never experienced headache</i>		<i>Have experienced headaches, but not MO</i>		<i>Possible MO</i>		<i>MO</i>		
		<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	<i>n</i>	<i>%</i>	
Ancestry (multiple responses permitted)	European	251	74	27	6	112	78	43	72	69	73	.162
	African	98	29	14	32	39	27	18	30	27	29	.939
	Asian	33	10	6	14	13	9	6	10	8	9	.794
Employment	Employed	283	83	33	75	124	87	50	83	76	81	.300
	Students	84	25	10	227	33	23	19	32	22	23	.583
Highest level of education	Tertiary	32	9	42	95	132	92	54	90	81	86	.273
	Secondary	309	79	2	5	11	8	6	10	13	14	
Home language	English	177	52	25	57	71	50	30	50	51	54	.035
	Afrikaans	126	37	8	18	58	41	25	5	35	37	
Sex	Female	268	79	28	64	104	73	51	85	85	90	.001
	Male	72	21	16	36	38	27	9	15	9	10	

7.5.2 Health.

There were no significant differences between the four groups for medication overuse or number of cigarettes smoked. However, the groups did differ on the frequency of alcohol intake. Post-hoc analysis with Dunn-Bonferroni testing indicated that Groups 2 and 4 differed significantly ($p = .016$). Table 7-3 shows a summary of the health data and the p-values for between-group comparisons. Here the groups did differ significantly on the number of members that reported head or neck injuries

Table 7-3**Frequencies (*n*, % of group) of health information and comparisons across groups**

<i>Variable</i>	<i>Total sample</i> (<i>N</i> = 341)		<i>Group 1</i> (<i>n</i> = 44)		<i>Group 2</i> (<i>n</i> = 143)		<i>Group 3</i> (<i>n</i> = 60)		<i>Group 4</i> (<i>n</i> = 94)		<i>p</i>
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Bleeding disorders	15	4	3	7	4	3	1	2	7	7	.185
Brain infection	13	4	0	0	4	3	3	1	6	6	.065
Cancer	14	4	1	2	5	4	4	7	4	4	.895
Degenerative disorders	6	2	1	2	5	4	0	0	0	0	.342
Head or neck injury	18	2	6	14	9	6	10	17	36	38	<.001
Psychiatric disorders	56	16	7	16	20	14	9	15	20	21	.316
Seizures	6	2	0	0	3	2	1	2	2	2	.884
Stroke	5	2	2	5	1	1	0	0	2	2	.176
Terminal illness	2	1	1	2	1	.1	0	0	0	0	.211

7.5.3 Health-related quality of life, temperament, coping and social support.

The central tendencies and comparisons across the groups for the psychological data are shown in Table 7.4. These results are discussed under the separate headings that follow. Scores of the TPQ are shown for the four separate categories. The maladaptive coping strategy of catastrophizing is not prominent, with the mean score for the PCS at 4.264 *SD* = 4.269 for the full sample. The highest score possible here is 20. The index for amount of social support in the full sample is 4.029 *SD* = 1.753. The highest possible score for this index is 9. Though the amount of social support perceived by the groups does not differ significantly, there are significant differences in terms of HRQOL, HA and the PCS 4 Item score.

Table 7-4: Means, standard deviations and comparisons across groups of psychological data

<i>Variable</i>	<i>Total sample</i> (<i>N = 341</i>)		<i>Group 1</i> (<i>n = 44</i>)		<i>Group 2</i> (<i>n = 143</i>)		<i>Group 3</i> (<i>n = 60</i>)		<i>Group 4</i> (<i>n = 94</i>)		<i>p</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
SF-12 Index	.731	.126	.743	.149	.763	.112	.718	.132	.687	.117	< .001
NS	14.557	5.541	14.023	4.901	14.126	5.721	15.7	5.646	14.734	5.444	.121
HA	14.815	7.599	12.25	6.613	13.511	7.163	16.45	7.425	16.957	8.091	< .001
RD	17.434	4.644	17.523	5.781	17.161	4.442	17.583	4.077	17.713	4.747	.802
P	5.821	1.908	5.728	2.336	5.664	1.8	5.75	1.772	6.149	1.923	.117
Pain coping Scale	4.264	4.269	6.429	6.272	2.210	2.868	5	4.17	6.596	4.316	< .001
Amount of social support (index)	4.029	1.753	3.957	2.054	4.288	1.810	3.886	1.826	3.761	1.408	.187

7.5.4 Health-related quality of life.

The group with the lowest HRQOL was the MO group ($M = .687$, $SD = .117$), followed by the possible MO group, then the group that had never experienced a headache. The non-MO headache group experienced the highest HRQOL of the four groups ($M = .763$, $SD = .112$).

Significant differences were found between the four groups on HRQOL ($p < .001$). Post-hoc Dunn's testing with Bonferroni correction showed significant differences between Group 1 (never experienced a headache) and Group 4 (those with MO) ($p = .035$) and between Group 2 (non-MO headache sufferers) and Group 4 ($p < .001$). Thus, the MO group had significantly poorer HRQOL than both non-migraine groups, but not significantly different HRQOL from the possible MO group.

7.5.5 Temperament and coping.

Significant differences were found between the four groups on HA and PCS ($p < .001$). Post-hoc Dunn's testing with Bonferroni correction was conducted. This showed the significant differences on HA to be between Group 1 (never experienced a headache) and Group 3 (possible MO) ($p = .022$); between Group 1 and 4 (those with MO) ($p = .003$); and between Group 2 (non-migraineurs) and 4 ($p = .007$). HA is highest amongst those with MO ($M = 16.957$, $SD = 8.091$) and was closely followed by HA amongst possible MO sufferers ($M = 16.45$, $SD = 7.425$), without significant difference between the two groups. Pain coping scores differed significantly between Group 1 and 2 ($p = .034$), Group 2 and 3 ($p < .001$) and between Group 2 and 4 ($p < .001$). The migraineurs thus employ the maladaptive coping strategy of catastrophizing significantly more than those not suffering from MO.

7.6 Correlations

Correlations were calculated using Spearman's rho and controlling for language, sex, frequency of alcohol intake and head or neck injury (see Figure 7-1). Significant correlations with small effect sizes (Cohen, Manion, & Morrison, 2011) were found between HA and Catastrophizing ($r_s = .222, p < .001$) and the Amount of social support and Catastrophizing ($r_s = -.176, p < .001$). A significant correlation with moderate effect size is seen between HA and the Amount of social support ($r_s = -.307, p < .001$).

A small effect size is also seen in the significant correlation between the Amount of social support and HRQOL ($r_s = .210, p < .001$). This shows that more perceived social support increases HRQOL. HA is also significantly correlated with HRQOL ($r_s = -.390, p < .001$), indicating that the higher the HA, the lower HRQOL. The effect size is moderate. The significant correlation between HRQOL and maladaptive pain coping (Catastrophizing) approaches a large effect size ($r_s = -.414, p < .001$). This shows that lower use of catastrophizing is related to better HRQOL.

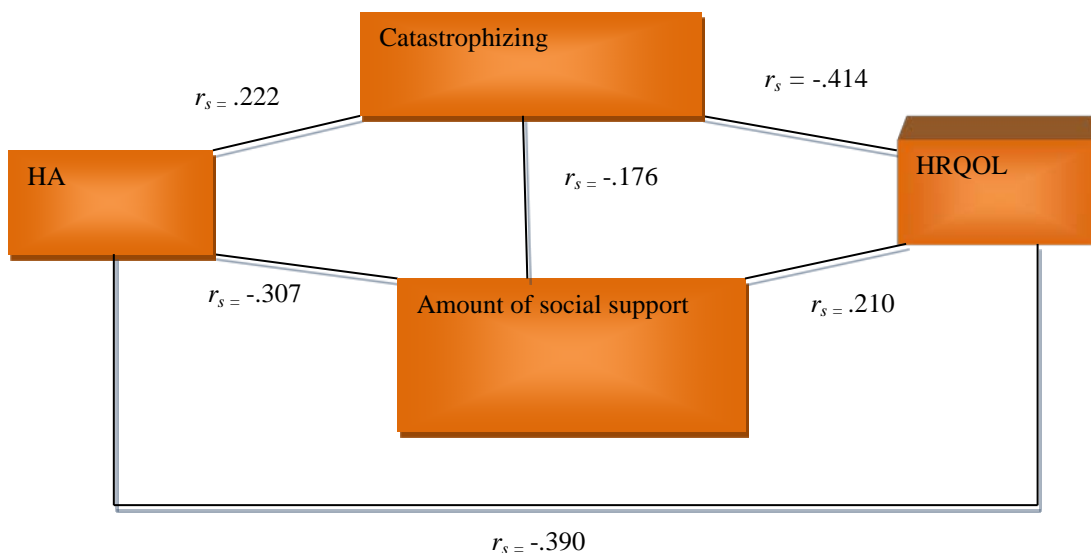


Figure 7-1: Correlations between psychological variables ($N = 341$)

*All correlations controlled for sex, language, frequency of alcohol intake and head or neck injury; all significant at $p < .001$

7.7 Predicting health-related quality of life

The potential relationship between temperament, neurotransmission profile, coping strategy and perceived social support was explored. The analysis was directed at understanding which variables could significantly account for variance in HRQOL. Neurotransmission is only examined in the next chapter.

7.7.1 Linear regression.

In order to determine whether HRQOL could be predicted using the psychological data, regression analysis was conducted. Before conducting the regressions, the following assumptions were checked: (i) Linearity, (ii) normal distribution of the residuals, (iii) homoscedasticity (Field, 2013). As indicated in Table 7-5, the correlations between HRQOL and the three potential predictors are significant even when not correcting for those variables presented in in section 7.8.3. The correlations between Catastrophizing and HRQOL and HA and HRQOL are moderate, while the correlation between HRQOL and the amount of social support is weak. Nevertheless, the correlations do indicate a linear relationship between the variables, which satisfies the first assumption.

Table 7-5: Correlations between HRQOL, pain coping, social support and temperament

SF-12 Index	Statistic	Catastrophizing	Amount of Social support	HA
	<i>r</i>	-.436	.171	-.412
	<i>p</i>	.000	.002	.000
	<i>N</i>	311	340	341

Q-Q plots were generated for HRQOL, Catastrophizing, Amount of social support and HA. Visual inspection of the graphs showed good fit. The non-parametric Levene's test for

non-normal distribution was used to determine homoscedasticity. The result was significant ($p < .001$), indicating that the third assumption was met for this data.

Power was explored using the G*Power software (<http://www.gpower.hhu.de/en.html>). For medium effect size, a sample of 77 would have been required, thus the sample is sufficient for this regression.

The 30 participants that never experienced a headache were excluded from analysis. Outliers were identified using cut-off scores for Mahalanobis, Cook's and Leverage. Two cases were outliers for two of the three calculations and were excluded from mediator and moderator analysis.

Aside from the several assumptions examined before linear regression was used, there are a few more assumptions to be tested in order to decide if a model can be generalised beyond this sample. These are (iv) Errors must be independent, (v) There should be no perfect multicollinearity (vi) Variables must be quantitative and the outcome variable must be continuous (Field, 2013). Independence of errors was investigated using the Durbin-Watson test. The Durbin-Watson statistic was 1.746, which indicates that error terms are independent. Tests of multicollinearity were below 2, indicating that multicollinearity is not a problem. The variables used in the regression are all quantitative and HRQOL as measure on the SF-12 Index is a continuous variable. Therefore the regression model is potentially generalizable outside of this sample.

Hierarchical regression was utilised to control for the effect of sex, language, frequency of alcohol intake and head or neck injury. Regressions were run with HRQOL (SF-12 index) as the dependent variable (Models 1 and 2). The results are shown in Table 7-6. The model explained 29% of the variance in HRQOL scores, $R^2 = .292$, $F(3, 301) = 37.130$, $p < .001$. Although HA and Catastrophizing both contributed significantly to the model ($p < .001$), social support did not ($p = .232$).

Table 7-6: Summary of the hierarchical regression analysis for variables predicting health-related quality of life with regression coefficients (beta weights), proportions of variance accounted for (adjusted R^2) and changes in R^2 (ΔR^2) with SF-12 Index scores as dependent variable ($n = 308$)

<i>Model</i>		<i>Unstandardized Coefficients</i>		<i>Standardized Coefficients</i>	<i>t</i>	<i>p</i>	
		β	Std. Error	β			
1 HRQOL as dependent variable							
	Sex	-.048	.018	-.154	-2.751	.006	
	Language	-.004	.003	-.073	-1.301	.194	
	Head injury	.041	.017	.136	2.422	.016	
	R^2						.039
	ΔR^2						.048
2 HRQOL as dependent variable							
	Sex	-.022	.016	-.069	-1.390	.166	
	Language	-.003	.003	-.042	-.871	.385	
	Head injury	.028	.015	.090	1.860	.064	
	Catastrophizing	-.010	.002	-.337	-6.685	.000	
	Amount of Social support	.004	.004	.061	1.197	.232	
	Harm avoidance	-.005	.001	-.293	-5.607	.000	
	R^2						.292
	ΔR^2						.257

7.7.2 Mediation and moderation effects.

Mediation and moderation were investigated using the Hayes' Process Model (Hayes, 2013). The tool provided by Hayes was downloaded and used in SPSS. Sex, frequency of alcohol intake, head and neck injury and home language were used as covariates in all calculations to control for possible effects.

Moderation effects (Process Model 1) were investigated using catastrophizing as the outcome, with HA as the predictor and average headache pain severity, amount of social

support, headache frequency and medication overuse as potential moderators. No significant moderation effects were found.

Mediation effects (Process Model 4) were investigated for the relationship between HA and Catastrophizing, testing average headache pain severity, amount of social support, headache frequency, frequency of alcohol intake and medication overuse as possible mediators. Only partial mediation effects were noted. A summary of the mediation effects is shown in Table 7-7.

Table 7-7: Summary of results for the mediation analyses for the prediction of Catastrophizing by Harm avoidance

<i>Mediator</i>	<i>Partially standardized indirect effect</i>		<i>Completely standardized indirect effect</i>		<i>z</i>	<i>p</i>
	<i>β</i>	<i>Standard error</i>	<i>β</i>	<i>Standard error</i>		
Headache pain intensity	.006	.003	.046	.020	2.019	.043
Headache frequency	.008	.003	.062	.022	2.799	.005
Amount of social support	.009	.004	.066	.031	2.281	.023

Average headache pain severity.

In the first step of the mediation model, HA significantly predicted average headache pain severity, $b = .396$, $t(300) = 2.051$, $p = .041$. The average headache pain severity significantly predicted Catastrophizing, $b = .092$, $t(299) = 12.661$, $p < .001$. The third step of the mediation was the regression of HA on Catastrophizing, controlling for average headache pain severity, and this was also significant $b = .071$, $t(299) = 2.679$, $p = .008$. The regression of HA on Catastrophizing was however still significant when not controlling for the mediator, $b = .108$, $t(300) = 3.347$, $p = .001$. The Sobel test did confirm a partial mediation effect, though ($z = 2.019$, $p = .043$).

Headache frequency.

HA significantly predicted headache frequency, $b = .046$, $t(300) = 3.412$, $p = .001$. Headache frequency significantly predicts Catastrophizing, $b = .794$, $t(299) = 5.099$, $p < .001$. The third step of the mediation was the regression of HA on Catastrophizing, controlling for headache frequency, and this was also significant $b = .073$, $t(299) = 2.353$, $p = .019$. As previously reported, this relationship remained significant when not controlling for the mediator, though. The Sobel test again indicates a partial mediation effect for headache frequency ($z = 2.799$, $p = .005$).

Amount of social support.

HA significantly predicted the Amount of social support, $b = -.073$, $t(300) = -6.147$, $p < .001$. Amount of social support significantly predicted Catastrophizing, $b = -.346$, $t(299) = -2.488$, $p = .013$. The third step of the mediation was the regression of HA on Catastrophizing, controlling for headache frequency, and this was also significant $b = .082$, $t(299) = 2.417$, $p = .016$. Once again, this relationship remained significant when not controlling for the mediator, though. The Sobel test again indicates a partial mediation effect for headache frequency ($z = 2.281$, $p = .023$).

The results of the hierarchical regressions and mediation analyses were combined to form a single figure. The resulting model is depicted in Figure 7-2. Though the figure represents a potential path diagram for HRQOL in MO, path analysis was not conducted as there were insufficient MO cases to justify such analysis (Kline, 2011).

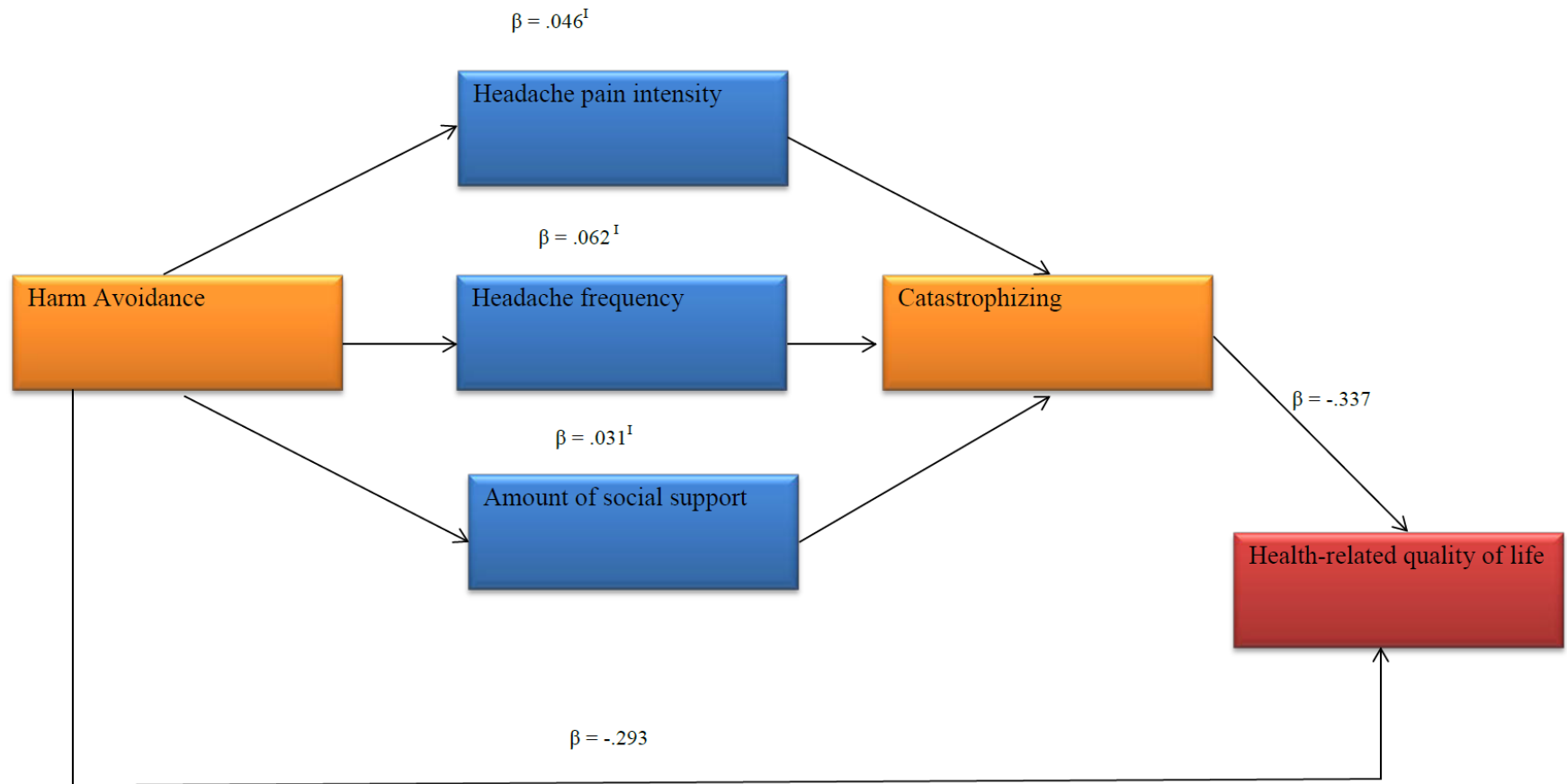


Figure 7-2: Model summary for regression analysis predicting HRQOL when controlling for sex, head and neck injury and language. Red indicates the outcome variable, yellow the original predictors and blue the emergent partial mediators. Numbers are standardized beta coefficients, significant at $p < .05$. ^Irepresents the indirect effect.

7.8 Conclusion of Chapter 7

Over a year, 341 adult residents of Gauteng Province, South Africa completed the survey of headache symptoms, temperament, pain coping and social support. A total of 154 (46%) met the criteria for MO or possible MO. Home language and sex emerged as significantly different between those with MO or possible MO and those without. HA and the pain coping strategy of catastrophizing were significant predictors of HRQOL, even when controlling for sex, language, frequency of alcohol intake and head or neck injury.

Chapter 8: Results of Phase 2

The data from phase 2 of the study are presented in this chapter. This begins with attrition rate, which is followed by the comparisons between the migraine without aura (MO) and non-migraine participants (NM) groups. The comparisons of the two groups (on demographic and health variables) were conducted for two reasons: To establish whether or not the subsets differed significantly from the larger sample ($N = 341$) and to determine if the serum glutamate subset ($n = 66$) differed significantly from the transporter expression subset ($n = 20$). This was necessary for determining if the results from the studies of the two subsets were generalizable to the larger study. The phase 2 data were then used to determine the contribution of biological predictors to health-related quality of life (HRQOL) in MO.

8.1 Data collection for Phase 2

Of the 341 participants that completed the survey, 164 granted permission to be contacted for the collection of blood. Invitations were sent via e-mail to these participants to inform them of the details of specimen collection. Follow ups were made via e-mail, SMS and telephone between October 2015 and February 2016. Of these 164 participants, eight withdrew because of poor health and two had relocated to other countries.

Participants reported once-off for blood collection over a period of five months. Participants could choose to visit one of four Ampath depots for collection or to have the phlebotomist come to place of employment. A total of 66 participants (19%) donated blood. The high attrition could not be accurately accounted for as 10% of the missing 98 participants did not reply to any form of contact. A detailed discussion of the possible reasons for this outcome is undertaken under the section on methodological limitations in Chapter 9.

The 66 participants were divided into two groups: NM ($n = 23$) are those participants that do not meet the criteria for MO (people that have never experienced a headache and those whose headaches do not meet at least three of the ICHD-II criteria for MO, as explained in

chapter 7) and the MO group (made up of participants that met either the criteria for MO or possible MO, according to the ICHD-II criteria, $n = 43$). Concentration of serum glutamate was examined in all 66 participants' samples. All 66 samples underwent the RNA extraction. However, only 26 samples yielded results from the SLC1A2 expression analysis (this attrition was due to quality control steps and is explained in Chapter 6 under the section on transporter analysis). Six of the 26 SLC1A2 samples yielded differences in C_t values for the reference and target genes less than six, which suggested a problem with contamination (Qiagen, 2011a) and these were therefore omitted. Given that the psychological, ELISA and qPCR data were gathered on different sized groups, it was important to examine the demographic, health and psychological data for varying patterns at each stage.

8.2 Demographic differences between the migraine without aura and non-migraine participants groups

The NM and MO groups were compared for significant differences on age, home language, sex, heredity, employment and frequency of alcohol intake. No significant differences were noted in either the ELISA ($n = 66$) or the qPCR study ($n = 20$). It can be inferred therefore that the sub-samples are similar to one another. However, the significant differences between MO and NM groups that were seen in the larger sample ($n = 341$) are not reflected in these sub-samples: The larger sample ($n = 341$) showed significant differences regarding the distribution of home language ($p = .035$) and sex ($p = .001$). This does suggest that the results of the smaller sample studies should be interpreted cautiously when making inferences about the larger sample.

8.3 Health differences between the migraine without aura and non-migraine participants groups

The two groups were compared against one another for differences in their physical and psychological health histories. They were also compared on the health indicators of fasting glucose, total cholesterol and intrinsic clotting efficiency.

The only significant difference on medical / psychological history was noted with the previous diagnosis of headache disorders ($p = .025$), in which the MO group had 18 previous diagnoses and the NM group only four ($n = 66$). This differs from the results of the group comparisons of the larger sample ($n = 341$) in which a significant difference was only seen with respect to head and neck injuries ($p < .001$). Once again, this indicates that some caution should be exercised when trying to generalise the smaller sample results to the larger sample.

Table 8-1 shows the medical screening data for the two groups. The groups did not differ significantly on fasting glucose, total cholesterol or clotting indicators.

Table 8-1: Fasting glucose, total cholesterol, intrinsic clotting and serum glutamate levels of the migraine without aura ($n = 43$) and non-migraine participants groups ($n = 23$)

	<i>MO (n = 43)</i>			<i>NM (n = 23)</i>			<i>P</i>
	<i>M</i>	<i>SD</i>	<i>Mdn</i>	<i>M</i>	<i>SD</i>	<i>Mdn</i>	
Fasting glucose (mmol/l)	5.291	.798	5.1	5.33	.773	5.2	.762
Total cholesterol (mmol/l)	5.023	0.974	4.900	5.048	0.896	5.100	.666
Clotting (aPTT ratio)	0.958	0.103	1.000	0.952	0.090	1.000	.762
Serum glutamate (µg/ml)	23.719	17.649	18.440	26.582	15.948	21.935	.933

8.4 Biological variables selected for predicting HRQOL

The two biological variables selected as potential predictors of HRQOL in this study were serum concentration of glutamate and the level of expression of glutamate's main transporter, SLC1A2. The study of serum glutamate concentration was conducted on 23 controls and 43 MO participants. The SLC1A2 qPCR yielded data for five NM and 15 MO participants.

8.4.1 Glutamate concentration.

Glutamate concentration for the sample ($n = 66$) was within the normal range for healthy people (Abnova, n.d.) at $24.718 \mu\text{g/ml}$ ($Mdn = 18.755$, $SD = 17.007 \mu\text{g/ml}$). Table 8-2 shows the central tendency data for the two groups. The NM have higher glutamate levels than the MO group. However, there was no significant difference between the two groups on glutamate concentration ($p = .933$).

8.4.2 SLC1A2 expression.

Figure 8-1 shows the median Ct values for normalized SLC1A2 expression for the two groups. The expression of SLC1A2 is higher amongst the NM. However, the difference in the Ct values between the two groups is not statistically significant ($p = .168$).

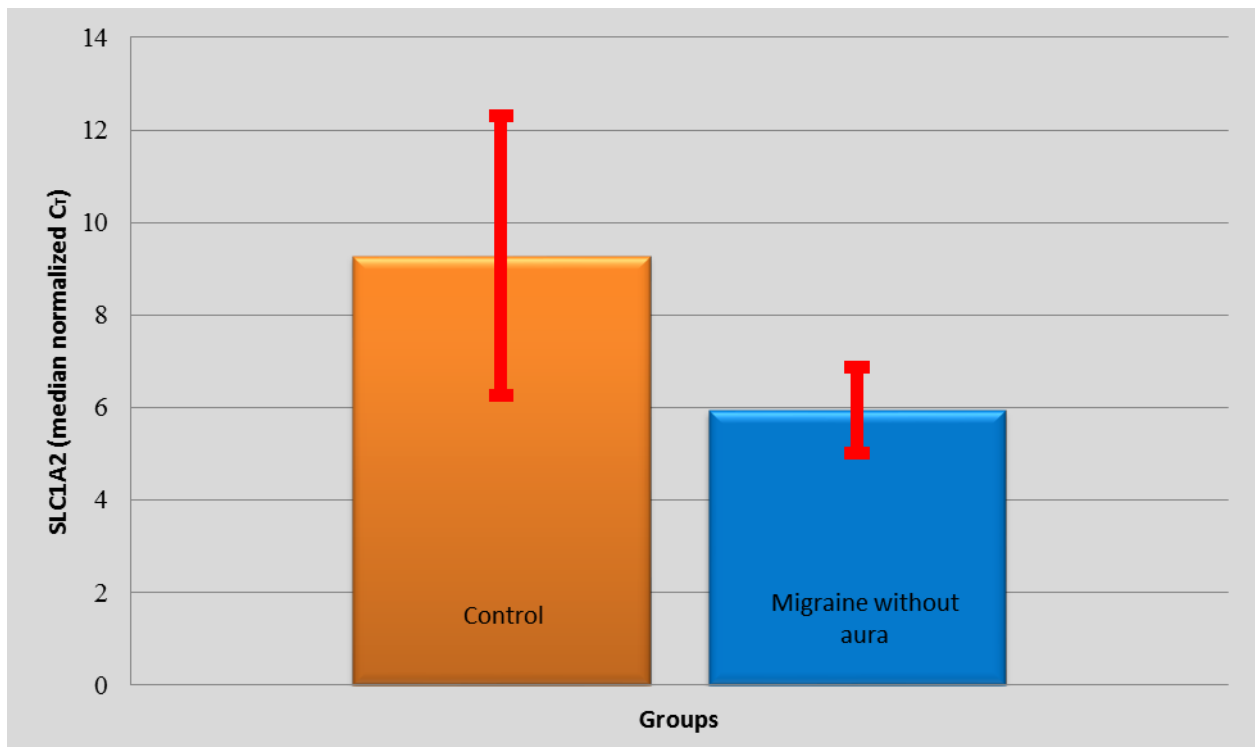


Figure 8-1: Relative expression of SLC1A2 of the migraine without aura ($n = 15$) and NM groups ($n = 5$)

8.5 Correlation analysis

Table 8-2 shows the correlations for the smaller study. Only the relationships to HRQOL were examined: The correlations remain significant (as they were for the larger sample, $N = 341$) and in the same directions for HA and HRQOL ($r = -.414, p = .001$), Catastrophizing on the Pain Coping Scale and HRQOL ($r = -.380, p = .002$) and the amount of social support and HRQOL ($r = .290, p = .018$). No significant correlations were seen with the glutamate ELISA and qPCR data and any of the psychosocial variables. There were also no significant correlations seen between the ELISA and qPCR data.

Table 8-2: Correlation matrix for psychosocial and biological variables ($n = 66$ except for SCL1A2 where $n = 23$)

		<i>NS</i>	<i>HA</i>	<i>P</i>	<i>RD</i>	<i>SF-12 Index</i>	<i>Pain coping Scale</i>	<i>Amount of social support (index)</i>	<i>Serum glutamate concentration</i>	<i>SLC1A2 (fold change)</i>
<i>NS</i>	r	1	-.101	-.16	.149	-.037	.223	.069	.003	.159
	p		.418	.2	.233	.766	.081	.579	.982	.503
<i>HA</i>	r	-.101	1	-0.014	.084	-.414**	.229	-.325**	.101	-.003
	p	.418		0.913	.503	.001	.073	.008	.421	.99
<i>P</i>	r		-.014	1	.529**	-.012	.007	.014	-.143	-.032
	p		.913		0	.925	.959	.913	.251	0.895
<i>RD</i>	r			.529**	1	-.114	.106	.098	-.053	-.391
	p			0		.36	.411	.433	.67	.89
<i>SF-12 Index</i>	r				-.0114	1	-.380**	.290*	-.016	.142
	p				0.36		.002	.018	.896	.055
<i>Pain coping Scale</i>	r					-.380**	1	-.301*	.164	-.026
	p					.002		.017	.203	.0918
<i>Amount of social support (index)</i>	r						-.301*	1	.025	-.276
	p						.017		.843	.238
<i>Serum glutamate concentration</i>	r							.025	1	.144
	p							.843		.544
<i>SLC1A2 (fold change)</i>	r								.144	1
	p								.544	

8.6 Regression analysis

Power was explored using the G*Power software. Unfortunately, the small sample ($n = 66$) is not sufficient to detect an effect size at anything above power of .14 for regression.

No regression analysis was therefore conducted.

8.7 Conclusion of Chapter 8

A set of participants ($n = 66$) chose to supply blood specimens for analysis for phase 2 of this study. Examination of serum glutamate concentration via ELISA showed that there is no significant difference between MO and NM participants in the amount of glutamate detectable in their serum. In addition, the qPCR analysis of 26 of the participants also did not yield significant group differences. The psychological data did not correlate significantly with either of these biological data points.

Chapter 9: Conclusion

This chapter provides a final, integrated discussion of the most important results of the research, as they pertain to the aims and research questions. Briefly, the study aimed to compare the health-related quality of life (HRQOL) of migraine without aura (MO) sufferers and NM; to explore the association between temperament and pain coping in MO and to examine how neurotransmission, temperament, pain coping, perceived social support (with consideration of lifestyle factors) contribute to the HRQOL experienced in MO. The three research questions addressed were: (i) In what way does the HRQOL of MO sufferers differ from the HRQOL of those without MO? (ii) What is the relationship between the harm avoidance (HA) temperament category and catastrophizing in MO? (iii) To what extents do temperament, neurotransmission profile, coping strategy and perceived social support explain the variance in HRQOL in MO? Following the discussion of the main findings, the limitations of the thesis are described in order to provide suggestions for future research. The chapter concludes with the contributions of the work to research, public health and clinical practice.

9.1 Comparing health-related quality of life

From the literature it is clear that answers to the first research question have been pursued extensively in Europe, North America and Asia, where migraine is acknowledged as a highly incapacitating primary headache disorder (Leonardi et al., 2005; Steiner, Stovner, & Birbeck, 2013). Sufferers experience intense pain with variable response to medication (Chia, Lim, & Wang, 2003). Aside from the pain of the attack, migraineurs also have to cope with the high cost of treatment, stigma, absenteeism and the many knock-on effects of these consequences of their disorder (Aydemir, Özkara, et al., 2011; Breslau & Davis, 1993b; Katsarava & Andre, 2011). For many migraine sufferers there is a significant effect on health-related quality of life (HRQOL)

(D'Amico et al., 2015; Dalhof & Dimenas, 1995; Hazard et al., 2009; Hung, Wang, Yang, & Liu, 2008; Kolotylo & Broome, 2000).

HRQOL is recognised as a vital aspect of patient care as the understanding grows that the impact of both the illness and the intervention on the individual extends beyond the body to all aspects of wellbeing (Addington-Hall & Kalra, 2001). The results indicate significant differences between MO participants and NM ($p < .001$). People that had never experienced a headache and those without MO headaches had higher HRQOL on the SF-6 than those with MO or possible MO. The MO group thus had significantly poorer HRQOL than non-MO sufferers. These results confirm those found in previous studies on migraine and control groups (Aydemir, Özkara, et al., 2011; Kolotylo & Broome, 2000).

To further contextualise this lower HRQOL, consider the following: The HRQOL for the MO participants in this thesis (indicated by the SF-12 Index score of the SF-6) was $M = .687$ $SD = .117$. The mean score for a non-institutionalised adults living in the United States of America ($N = 54\ 995$) ranges from .857, 95% CI [.851-.862] for those in their 20s to .742, 95% CI [.723 - .761] for octogenarians (Janel Hanmer, Lawrence, Anderson, Kaplan, & Fryback, 2006). In a general population study in Greece ($N = 1005$), the mean SF-6 score was .759, 95% CI [.750 - .768]. Meanwhile, a Brazilian study ($N = 5000$) showed that the mean SF-6 score was .82 $SD = .15$. The MO score in this thesis was well below the American, Greek and Brazilian data, which is not unexpected for a disorder that is known to impact so many aspects of well-being (Aydemir, Ozkara, et al., 2011; Dalhof & Dimenas, 1995; Leonardi et al., 2010; Martin et al., 2000).

However, what was not expected was the severity of the impact of MO. The HRQOL for people with MO is more comparable with the data from British liver transplant patients 12

months post-transplant $M = .615$, 95% CI [.570 - .652] (Longworth & Bryan, 2003); Dutch post-coronary artery bypass graft (CABG) patients $M = .62$ (SD not reported) (Stel & Buskens, 2006); or even Japanese people ($N = 1143$) older than 70 years $M = .674$ $SD = 0.137$ (Shiroiwa et al., 2015).

There are a number of implications of these findings. First and foremost, they raise concern about the amount of suffering Gauteng MO patients are subjected to in their daily lives. When exploring the components of HRQOL one is reminded that poor HRQOL translates into difficulties negotiating many aspects life, including physical and social activities, emotional regulation, pain and mental health (Ware, 2004; Ware & Sherbourne, 1992).

If MO has such a profound and pervasive effect on an individual's daily life, the effects on the individual's other related systems are likely to be significant as well. The effects of migraine on family, work and socio-economic spheres were highlighted in Chapter 1: Migraine causes great strain on the spousal and parental subunits and can disrupt daily family life very severely, even contributing to divorce or separation (Lipton et al., 2003; Smith, 1998). Migraine sufferers are less productive at work and are frequently absent from their jobs because of migraine symptoms (Gerth et al., 2001; Lantéri-Minet et al., 2003; Lipton & Bigal, 2005; Osterhaus et al., 1992; Rasmussen et al., 1995; Rasmussen, 1995; Unger, 2006; Shuu-jiun Wang, 2003). Furthermore, the monetary costs of migraine runs into billions of dollars in the United States and billions of Euros in Europe (Linde, 2006; Norton et al., 1999).

All clinicians would do well to assess each patient's perception of their HRQOL and to examine which aspects of the MO sufferer's life would benefit from intervention. The level of intervention for migraine therefore needs to be extended beyond medical treatment to include family therapy (Payne & Norfleet, 1986; Rosenstock & Cambor, 1979) and more practically-

focused psychoeducation and occupational therapy interventions - none of which appear to be a frequently offered option for MO patients, judging from the lack of peer-reviewed publications on such interventions.

9.2 Predictors of health-related quality of life in migraine without aura

For migraine researchers such as Kröner-Herwig, Morris, and Heinrich (2008), Martin (2007) and Newton (2008) there is particular usefulness in approaching migraine questions from a biopsychosocial perspective. The biopsychosocial approach allows the integration of a number of potential HRQOL determinants into a single project within a coherent framework. Thus, the biopsychosocial approach was considered a pragmatic approach to attempting to answer the questions about predictors of HRQOL in migraine and this thesis was framed in this biopsychosocial approach.

In examining the role(s) of temperament, perceived social support, pain coping and glutamate in MO HRQOL, the researcher tried to discern the pattern of how the genomic, molecular, cognitive, emotional and behavioural may interact to allow one individual suffering immense pain to enjoy a high HRQOL, while another might not.

As discussed in Chapter 2, one of the challenges of this biopsychosocial study of migraine was that there are neither psychological, nor biological markers for migraine. However, neither biomarker, nor psychological candidates are in short supply (Abbate-Daga et al., 2007; Loder et al., 2006; Mongini, Fassino, et al., 2005; Sánchez-Román et al., 2007; Tietjen et al., 2010b), which complicated the choice of factors to investigate in this study. In the biological study of migraine, glutamate is purported to be a major player in migraine pathogenesis, though the mechanism is still under investigation (Anttila et al., 2010; Cananzi, D'Andrea, Perini, Zamerlan, & Welch, 1995; Ferrari, Spaccapelo, Pinetti, Tacchi, & Bertolini, 2009; Párdutz et al.,

2012; Schürks, 2012). Five major themes emerged from the psychologically-directed research into migraine: Temperament, parent-child relationships, adverse early life events, stress and coping. The connection between glutamate and psychological aspects of behaviour, cognition and emotion became evident through Cloninger's Psychobiological Model of Personality. As explained in Chapter 2, the temperament dimensions proposed by Cloninger are underpinned by four neurotransmitter systems - one of which is glutamate (Conrad et al., 2007; Hansenne et al., 1999; Mongini, Keller, Deregibus, Barbalonga, & Mongini, 2005).

As discussed in Chapter 4, there are numerous factors that can contribute to and detract from HRQOL in any disorder (Carod-Artal et al., 2009; Ho et al., 2010; Nestvold & Stavem, 2009; Ordu Gokkaya et al., 2012; Ritsner et al., 2006; Tajvar et al., 2008; Vilhena et al., 2014). Various predictors of HRQOL in MO (Lucas et al., 2006; Santanello et al., 2002) have also been proposed, including glutamate (Andreou & Goadsby, 2011; Freilinger, Anttila, Vries, & Malik, 2013), temperament (De Filippis et al., 2008), pain coping (Abbate-Daga et al., 2007; Chiros & O'Brien, 2011; Thorn et al., 2007) and social support (Cornish et al., 2009; Pragodpol & Ryan, 2013), which were examined in this thesis.

Thus, the literature on predictors of HRQOL across various disorders and then in migraine specifically revealed some overlap with psychological aspects of migraine research. In particular, temperament and coping (including social support) were foregrounded (Abu Bakar et al., 2016; Chang, 2004; Cornish et al., 2009; Pragodpol & Ryan, 2013; Sales et al., 2014). This is discussed in detail in Chapter 4. Thus, the focus of the thesis settled on how HRQOL in MO might be affected by glutamate, temperament, coping and social support.

HRQOL was significantly correlated with all three psychological variables ($p < .05$), but with neither of the biological variables. The correlations between HRQOL and Catastrophizing

($r = -.436, p < 0$) and HRQOL and HA ($r = -.412, p < 0$) are both moderately strong. This suggested that HRQOL would be decreased significantly if the MO sufferer has high HA or high catastrophizing tendencies. The weaker correlation between HRQOL and social support ($r = -.171, p = 0.002$) suggested that HRQOL could be increased if a MO sufferer has the perception of having more social support. Essentially, the perception of a higher level of social support may improve the outlook for a MO patient.

Significant predictors were found for HRQOL when controlling for sex, head and neck injury, frequency of alcohol intake and language. These two predictors are HA and Catastrophizing. The results of the regression analyses (mediation and hierarchical regressions) are depicted in Figure 7-2. The hierarchical regression model only accounts for 29% of the variance in HRQOL. In their study of 247 American women with migraine, Kolotylo and Broome (2000) showed that the chronicity of the pain, presence of depressive symptoms and the intensity of the headache pain accounted for 63% of the variance in HRQOL of the participants. Other researchers have also reported a central role for psychiatric disorders (Breslau & Davis, 1993b; Finocchi, Villani, & Casucci, 2010; Napolitano, 2008) in the HRQOL of migraine sufferers. This suggests that the addition of one or more psychiatric symptoms to the regression may be worthwhile.

9.2.1 The migraine personality revisited.

As discussed in Chapter 2, the maladaptive coping strategy of Catastrophizing is a prominent feature of the psychological functioning of people suffering from migraine (Abbate-Daga et al., 2007). Though it is difficult to infer causality from the available literature, it is possible to deduce at the very least that temperament has a role to play in how people with MO

develop Catastrophizing as a pain coping strategy (Compas, Connor-Smith, & Jaser, 2004; Hachaturova, 2010; Rueda & Rothbart, 2009).

Previous studies have highlighted the association between harm avoidance (HA) and migraine (Mongini, Fassino, et al., 2005; Sánchez-román, Téllez-Zenteno, Zermeño-phols, García-Ramos, & Guevara-López, 2007). This thesis confirms that HA is a feature of the MO sufferer's psychological makeup. In Chapter 7 the MO group not only displayed significantly higher HA scores than non-MO participants, but HA was significantly correlated with Catastrophizing ($r_s = .222, p < .001$). These results are interpreted with some caution as the effect size is small (Cohen, Manion, & Morrison, 2011).

HA is associated with traits such as worry, social shyness, pessimism and fatigability (Richman & Frueh, 1997). According to Conrad et al. (2007), HA in pain can be explained by the Fear-Avoidance model, which posits that individuals that are highly fear-avoidant will interpret pain in a catastrophic manner. This leads the individual to try and behave in ways that will result in circumvention of the pain. Unfortunately, these actions are ineffective and ultimately only worsen the pain. Moreover, pain sufferers that are highly harm avoidant also exhibit decreased pain thresholds and tend to rate their pain more intensely than those with lower HA (Park, Han, & Yang, 2006). When an individual has a heightened perception of pain as a threat to well-being, then she is more likely to evaluate the pain more negatively and to employ more passive coping strategies (Jackson, Wang, & Fan, 2014). Passive coping strategies are defined as maladaptive strategies, in which persons experiencing the pain allows the pain to affect their lives adversely or permit someone else to take over their roles and functions in response to pain (Jackson et al., 2014). This can include catastrophizing about pain.

Catastrophizing is seen as an exaggerated negative cognitive set toward pain in which a person will ruminate about the pain, magnify its significance and believe that he or she is helpless in relation to the pain (Lake, 2009). Thus, despite efforts to avoid pain, the highly HA individual has an exaggerated sense that any pain experience will be overwhelming (Sullivan et al., 2001). According to Sullivan et al. (2001) pain catastrophizing is consistently also associated with increased pain experience. This interaction represents a reciprocal relationship between HA and Catastrophizing.

Harm avoidance and Catastrophizing.

The preceding discussion answers the third research question about the variables involved in predicting HRQOL, but what about the specific relationship between HA and Catastrophizing that formed the second research question? When exploring this HA and Catastrophizing relationship in more detail, it was noted that, though the two were significantly correlated in this study when controlling for language, sex, frequency of alcohol intake and head or neck injury the relationship was weak ($r_s = .222, p < .001$). This relationship is partially mediated by how subjectively intense the headache pain is, how frequently the MO occurs and to how much social support the MO sufferer believes he or she has access. MO sufferers receiving adequate social support and experiencing fewer and less painful headaches are less likely to catastrophize their pain even if they have a high HA.

In Chapter 2 social support in migraine was discussed, while the potential role of social support in HRQOL was discussed in Chapter 4. Literature shows lower levels of satisfaction with perceived social support in migraineurs versus controls (Martin & Soon, 1993) and the importance of social support for mitigating the negative effects of migraine on HRQOL (Vos & Passchier, 2003). The effects of social support on migraine are sparsely documented, but studies

into chronic pain strongly suggest that social support can help decrease the psychological implications of the headaches, such as stigma and embarrassment (Davison, Pennebaker, & Dickerson, 2000), while also decreasing the level of acute pain experienced (Montoya, Larbig, Braun, Preissl, & Birbaumer, 2004; Montoya, Pauli, Batra, & Wiedemann, 2005)

Although social support did not emerge as a predictor HRQOL, it emerged as a partial mediator in the relationship between HA and Catastrophizing. These results suggest that the relationship between HRQOL and social support may be more indirect than previously thought. Martin and Soon (1993) suggest that more psychosocial elements of migraine require investigation. These could include aspects of religion, spirituality, sense of community or workplace satisfaction (Ben-Arye, Bar-Sela, Frenkel, Kuten, & Hermoni, 2006; Cohen & Koenig, 2003; Marks, 2010; Truchon & Fillion, 2000). The use of only one aspect (number of people available for supplying social support) of the Social Support Questionnaire (SSQ6) may have contributed to a limited exploration of social support and future studies should rather investigate both density of (number) and satisfaction with social support. Given the results of this thesis, more aspects of social support should be investigated not only for their direct effects on HRQOL in MO, but also for potential mediation and moderation of variables.

It is also noted that the pain experienced by the individual with MO and frequency of these headaches may play key roles in the relationship between HA and Catastrophizing in MO alongside social support. One interpretation of this finding is that limiting pain will limit the tendency to catastrophize – even if one has a high level of HA. Once again, patients may benefit from assessment of these constructs by their clinicians. While pain frequency and intensity are likely to be assessed at most visits to a medical practitioner, assessment of social support, temperament and coping mechanisms are not standard. While a review of the instruments

available for such assessments are beyond the scope of this study, there are short questionnaires available to measure temperament, social support and coping, including those utilised in this study.

9.3 What about glutamate and SLC1A2?

Perhaps the most surprising results for this thesis materialised from the biological data: Neither serum glutamate concentrations, nor relative expression of SLC1A2 differed significantly between MO and NM. The increasing amount of literature implicating glutamate in pain and in MO, which was reviewed in Chapter 2 (Alam et al., 1998; Andreou & Goadsby, 2011; Cananzi, D'Andrea, Perini, Zamberlan, et al., 1995; Ferrari et al., 1990; Lampl et al., 1999; Ramadan, 2003; Vikelis, 2007) could not be substantiated in this thesis.

These results are contrary to the expectation that MO sufferers would have higher glutamate levels than NM, contradicting the previous findings of differences in glutamate concentrations between migraine and control participants in plasma or CSF (D'Andrea & Leon, 2010; Vaccaro et al., 2007). Though the differences were not significant, the serum glutamate concentrations were actually higher amongst the NM ($n = 23$) than amongst the MO ($n = 43$) participants.

The differences across groups may simply not have been detected because of the small sample for the biological variable measures. On the other hand, the results may be another indication that glutamate is a more prominent feature of MA than MO (Pietrobon, 2005). However, this research made use of serum for the ELISA, whereas other researchers have found differences in plasma and CSF (D'Andrea & Leon, 2010; Ferrari, Spaccapelo, Pinetti, Tacchi, &

Bertolini, 2009; Mallolas et al., 2006), which could account for the differences in these observations.

The differences in glutamate concentration between the various sample sources could be due to a variety of factors and there are numerous considerations for choosing serum or plasma in analyses (Lundblad, 2008). The difference in results between this thesis and other publications indicates that further understanding is required of the release of glutamate in the clotting process. It may be more efficient to avoid serum glutamate analysis in future studies in favour of plasma, platelet or CSF. Serum glutamate levels may not be a suitable target for biomarker studies for the same reason. The plasma concentration of amino acids is well-correlated with, for example, nutritional status (Fadel et al., 2014) and is probably a more sensitive peripheral indicator of amino acid neurotransmitter concentration.

Though SLC1A2 expression was also not significantly different between the MO and NM, the transporter is more highly expressed in NM than in MO participants ($p = .168$). This is an interesting finding that should be explored further in a larger sample. Upregulation of SLC1A2 has been purported to play a protective role in glutamate excitotoxicity (Kanai & Hediger, 2003), indicating its potential value in therapeutic intervention in ischaemia. The implication of this finding is that it may be the efficiency of the glutamate cycle that determines allodynia and hyperalgesia in MO. The understanding of the mechanisms behind allodynia and hyperalgesia is constantly evolving and further work in this field is warranted with respect to migraine and the role of SLC1A2 in these processes.

9.4 Occurrence of migraine without aura

Although establishing the MO occurrence for Gauteng was not an aim of the thesis, it was an important by-product of the research. In Chapter 1 it was emphasized that prevalence data

is lacking for South Africa and so, the occurrence findings of this thesis were considered important enough to discuss in the conclusion.

In Chapter 7, occurrence was calculated by identifying participants that met all four MO criteria (criteria A-D) or any combination of three of the criteria (ABC, ABD, ACD or ABD). The occurrence of MO was 28% and 18% for possible MO. This is in stark contrast to the estimated 10% put forward for South Africa (Green, 2015) and the 10% reported in another African country, Ethiopia (Mengistu & Alemayehu, 2013).

9.4.1 A word of caution.

The first point to consider is that the sample is not random and one plausible explanation for this high occurrence is interest bias. Generalising of epidemiological findings should therefore be done cautiously.

Though one could speculate that the occurrence is elevated due to the absence of specific medical screening for comorbid disorders, self-reporting is an acceptable and widely used practice for population-based studies – as discussed in Chapter 2. Examination of participant blood tests (in the smaller study) for elevated cholesterol or fasting glucose and abnormal clotting profiles, revealed no significant differences between controls and MO participants in Chapter 8. This indicates that the MO sufferers were relatively healthy and medical screening may not have decreased the MO diagnoses significantly.

However, the high number of reported previous head injuries is difficult to ignore (46 of the 154 MO or possible MO participants). In the case definition put forward for this study in Chapter 2, it was explained that the relationship of the head injuries to MO could not be established through self-reporting for this research. There is literature to suggest that even mild head trauma should be investigated as a possible cause for headaches (Haas, 1996; Theeler &

Erickson, 2009). Most importantly for this thesis, the question of post-traumatic headaches has implications for the prevalence estimates.

9.5 Limitations of the study and suggestions for future research

The limitations of the research are discussed in terms of methodological shortcomings and the challenges presented by the processes involved in biopsychosocial research. Proposals are put forward for improved studies of this nature.

9.5.1 Methodological limitations.

The methodological limitations of this thesis are summarised with respect to its power, selection criteria, selection of participants and the choice of measures. These are discussed in the following sections and suggestions are put forwarded for future studies.

Statistical power.

The limited power of the thesis clear. The ideal would have been a large cohort study in which the initial survey sample number could have been sustained to the qPCR analysis stage, which would ideally have been substituted for a full gene expression analysis.

Future studies that do realise a larger sample and that undertake full gene expression analysis would require stricter application of the migraine criteria (Wang, Chen, & Fuh, 2010) and additionally stringent exclusion criteria. The aim of such exclusion criteria would be to assist in gathering information from a homogeneous sample. Suggested exclusions for future research are available in various migraine studies and summarised here: (i) Pregnant and lactating women and subjects with bleeding, clotting, terminal or degenerative diseases - based on good practice guidelines for protecting vulnerable subjects (Schwenzer, 2008). (ii) There is considerable controversy around the disorder migralepsy and how it is to be diagnosed and

classified (Verrotti, Coppola, Fonzo, & Tozzi, 2011). The inclusion of this migraine-triggered form of epilepsy would present unnecessary added complexity to data analysis. (iii) In addition, seizure events, whether provoked or spontaneous, can be of numerous origins, some of which overlap with other factors being related to the study of migraine study, such as abnormal blood sugar levels (Shneker & Fountain, 2003). Seizures may also be related to a history of acute neurological insult, which may include head trauma, infections such as meningitis and stroke (Shneker & Fountain, 2003). (iv) The relationship between stroke and migraine, although not clearly understood, is another potential confounding variable in migraine studies as it represents underlying vascular conditions such as vasospasm and arterial stiffness (Viola, Viola, Litterio, Buongarzone, & Fiorelli, 2012). (v) It may also be prudent to exclude subjects with hypertension: Both paroxysmal and malignant hypertension have been identified as causes of migraine (Agostini & Aliprandi, 2008). Although these data remain controversial, there is sufficient evidence that hypertension-migraine (Sarchielli, Mancini, & Floridi, 2007) could represent a peculiar subtype of the headache disorder. (vi) It should also be a consideration to exclude post-menopausal women from such a study as hormonal changes that occur during menopause have been implicated in the decreased frequency of migraine in women after the age of 50 years (Aegidius, Zwart, Hagen, Schei, & Stovner, 2007), yet the introduction of hormone replacement therapies into the life of a postmenopausal woman may have side effects, which include the worsening of migraine symptoms (Facchinetti, Nappi, Tirelli, Polatti, & Nappi, 2002).

Selection bias.

Selection bias is a factor limiting this research as the sample was mainly derived from Gauteng residents that were educated to tertiary level and had access to the internet. Future

studies should include participants further away from the two main cities of Gauteng (Pretoria and Johannesburg).

The selection bias was possibly increased by the decision of many participants not to give blood for laboratory assessment. More time may need to be spent on explaining this aspect of the research (Abu-Saad Huijjer & Abboud, 2013). It may be particularly useful to improve the discussion on the use of genomic data and the collection of blood for participants (Butali et al., 2015). In this thesis 98 participants stated that they were of African ancestry; only 11 of these participants volunteered to donate blood for analysis, which did raise a question about the role of history and cultural beliefs in volunteering for research in South Africa. In their research into perceptions of voluntariness in medical research, Barsdorf and Wassenaar (2005) interviewed 111 members of the South African public. They found that Black participants perceived medical research to be a less voluntary process than Indian and White South Africans ($p < 0.001$). This difference was independent of level of education, knowledge of medical research procedures and experience of medical research. Barsdorf and Wassenaar point out that it is important for South African researchers to bear in mind the historical context of apartheid, the legacy of racial mistrust and how this manifests in perceptions of personal agency, alongside factors such as lack of values clarification; general public perceptions about medical research and the treatment of subjects in developing countries. Though alluded to in Barsdorf and Wassenaar's (2005) investigation, the question of cultural beliefs is not explored here. It may be useful for future studies to focus on questions of how beliefs can influence participation. Cultural and religious beliefs can shape health beliefs, which can influence how people access or approach health services – including health-related research (Shavers-Hornaday, Lynch, Burmeister, & Torner, 1997). Decisions to donate organs (Randhawa, 1998), blood for transfusion (Copeman, 2009;

Zaller et al., 2005) or relatively small specimens for genetic testing (Wong, Chia, Yam, Teodoro, & Lau, 2004) are highly influenced by culture.

Choice of measures.

Undoubtedly there is a limitation in the choice of neurotransmitter investigated. Cloninger's theory implicates four major neurotransmitters (Cloninger, Zohar, Hirschmann, & Dahan, 2012; Gillespie et al., 2003; Verweij et al., 2010), but this study only examined one neurotransmitter. An extension of this research would be to examine the pattern of neurotransmission for the other three neurotransmitters (dopamine, noradrenalin and serotonin) (Matsumoto et al., 2007; Verweij et al., 2010).

A further logical extension of the work would be to triangulate data from various techniques. For example, temperament questionnaires other than the Tridimensional Personality Questionnaire (TPQ) could be used. Alternatively, normative data for the South African population could be established for the TPQ. Such data is already available for a number of other countries (Gana & Trouillet, 2003; Hansenne et al., 1999).

The serum ELISA could be replaced with gold standard quantification techniques such as amino acid analysis or LC-MS, while the single gene qPCR investigation could be optimised through the use of targeted array analyses (Vallejo-Illarramendi et al., 2006), or investigations of the glutamate-glutamine cycle (Hertz, 2013).

9.6 Contribution of this study

Despite its limitations, the thesis does make a valuable contribution to our understanding of migraine. As both a clinical and public health concern migraine has to be regarded from both epidemiological and clinical practice perspectives if society is to understand sufferers' needs and

plan and evaluate intervention (D'Amico et al., 2015) and this thesis starts addressing the fundamental need for epidemiological data in South Africa, while also exploring some of the factors that need to be taken into account for successful treatment. The key contributions of the thesis are discussed in terms of the biopsychosocial approach, intervention strategies for sufferers and the contributions the work makes to headache research and public health knowledge.

9.6.1 The usefulness of the biopsychosocial approach.

This thesis makes an important contribution to HRQOL literature through the use of a biopsychosocial approach. The work also makes an important contribution to growing literature on the integration of biological and psychosocial approaches in the exploration of pain, which has been on the increase for two decades (Norton, Asmundson, Norton, & Craig, 1999; Racine et al., 2012).

Given the relatively new emphasis on biopsychosocial studies of migraine (Kröner-Herwig et al., 2008; Martin, 2007), this research is an important addition to a growing field. Though emphasis on HRQOL is not new in migraine research (Caproni et al., 2015; D'Amico et al., 2015; de Velasco & Gonzalez, 2003; Freitag, 2007; Kolotylo & Broome, 2000), the biopsychosocial approach is novel. The biopsychosocial approach is considered a useful means of making sense of the volume of data already available on MO as it offers researchers the chance to put together various iterations of the existing information without necessarily reducing the complexity of emerging answers. To paraphrase Gatchel and Turk (2008), this is an example of using more complex means to improve understanding of the complex answers that have already been gathered.

Aside from contributing to an improved understanding of MO HRQOL, the use of a biopsychosocial approach in this thesis also integrates the research on a number of different levels as patient, scientist, molecular and social data are combined to offer various perspectives. While more information is not necessarily better, this approach does allow researchers, patients and health care providers to triangulate data. Triangulation still remains a powerful means of strengthening the reliability and validity of research.

This research data may be useful to clinicians as it indicates the potential usefulness of investigating both biological and psychological aspects of the MO patient's experience. MO sufferers are usually subjected to comprehensive medical examinations that emphasize the biological component of the disorder and medical treatments are then suggested accordingly. By introducing psychological assessment or even a brief psychological screening, the psychological burden of the disorder may be dealt with as well. Clinicians could offer such brief screenings in their own practices or refer the patient to a psychologist that works with pain-related disorders. Evidence to support the use of psychological assessment to plan treatment is found in the works of Martin (2008) and Turner and Houle (2013). The latter provide a useful review of the psychological constructs most often associated with headaches, which can help clinicians to understand the relationship between biological and psychological aspects of such pain.

9.6.2 Directions for possible interventions.

This thesis indicates a clear contribution of pain coping and temperament to MO HRQOL. If one turns this information to application in interventions, the results emphasize the importance of psychological involvement in managing migraine. A few peer reviewed publications have dealt with psychological interventions such as behavioural interventions and stress management techniques (Andrasik et al., 2009; Sieberg et al., 2012; Van Eeghem, 2005),

but much more work is required for strategies to be more widely accessible for patients and their health-care providers.

Facilitating change in the fearful and avoidant approach to pain that a MO patient may employ needs to become a central focus for interventions. Although temperament is considered stable over the lifespan (Calati et al., 2008), researchers acknowledge the potential impact of socio-cultural learning on temperaments. It is difficult to recommend specific intervention strategies for adjusting temperament, just as it is for changing personality structure. However, such interventions are documented (Chanen et al., 2008; Smith Benjamin, 1996).

This thesis shows that specific interventions for shifting catastrophizing coping tendencies are also likely to improve a sufferer's HRQOL. There is a large body of literature on the efficacy of interventions for adults in altering negative cognitive sets, with much of this literature focused on behavioural interventions of varying degrees of success (Kjøgx et al., 2016; Vranceanu, Hageman, Strooker, Vrahas, & Ring, 2015). However, it has been suggested that coping interventions would be more effective if pain acceptance is the focus, rather than instructing the patient in various coping strategies (McCracken, 1998; Rodero et al., 2011). Pain acceptance has been associated with decreased preoccupation with the pain and improved sense of competence as the pain sufferer becomes more motivated to participate in daily tasks (Lake, 2009).

9.6.3 Contribution to headache research.

The WHO has joined hands with three international non-governmental headache organizations to start a charity called *Lifting the Burden: The global campaign to reduce the burden of headache worldwide* (l-t-b.org, 2009). One of the concerns of the charity is that headache prevalence data is only partially detailed worldwide (Stovner et al., 2007). As

discussed in Chapter 1, peer-reviewed epidemiological data for South Africa is not available. One surmise is that prevalence in the country is similar to the estimated world prevalence of 10% (Green, 2015). This thesis therefore makes a key contribution to the campaign to decrease headache burden by providing epidemiological data that has been gathered in a systematic fashion.

The exclusive focus on MO in this thesis makes a very particular contribution to migraine research. In their systematic review of psychosocial challenges faced by migraineurs, Raggi et al. (2012) show that there is relatively little focus on MO versus MA. They also indicate that a number of studies investigate both MA and MO as a single entity and do not distinguish between them when reporting on HRQOL. This means that some of the nuances of MO are underexplored.

9.6.4 The significance for public health knowledge.

MO was shown to be a significant health concern for Gauteng residents in this thesis. The lack of research into the disorder will need to change if local public health systems are to adapt to public need. For example, only three (3%) of the participants meeting all four criteria for migraine ($n = 94$) reported having been diagnosed with a headache disorder. The occurrence data and the data on previous diagnosis raise questions about the lack of awareness of headache disorders in the Gauteng community.

The under-diagnosis of MO is perhaps not surprising given that headaches are underdiagnosed the world over (Lucas, Géraud, Valade, Chautard, & Lantéri-Minet, 2006; World Health Organization, 2012) and that South Africa has a number of more prominent health concerns with which it contends (Mayosi et al., 2009). The pattern of under-diagnosis was also previously well-illustrated in the FRAMIG 3 French population-based study (Christian Lucas et

al., 2006): A mere 40% of the 2 245 migraine sufferers were actually aware of their disorder. Lack of awareness translates into lack of effective treatment and untold suffering for 97% of the MO suffers in this study.

Such under-diagnosis also perpetuates the misperception that migraine has little impact on the individual or on society (Hazard et al., 2009). From the already-widespread literature (Hazard et al., 2009; Katsarava & Andre, 2011; Payne et al., 2011; Stokes et al., 2011) it is clear, though, that society cannot afford to ignore the individual, occupational and social impact of migraine.

9.7 Conclusion of thesis

This thesis proposed the involvement of two biological (glutamate and SLC1A2) and three psychosocial (temperament, pain coping and social support) variables in determining the HRQOL of people with MO. MO sufferers exhibited higher levels of the temperament dimension HA and the pain coping strategy catastrophizing than those without migraine. HA and Catastrophizing are significant predictors of HRQOL in MO. There were no significant associations detected for the two biological predictors.

These findings imply that there are specific psychological markers in MO. Migraine sufferers have been described as choleric in ancient times, and later, as neurotic. Most recently migraine sufferers have been shown to have high levels of harm avoidance tendencies and this was confirmed in this thesis. MO sufferers fear pain and believe that they will not be able to cope with their pain.

The roles of HA and Catastrophizing in predicting HRQOL for MO sufferers holds very important significance for MO interventions: The medical interventions for MO would be more beneficial for patient HRQOL if they were combined with interventions aimed at augmenting

coping and dealing with fears around pain. It is important to bear in mind that neither HRQOL nor headache pain are simple concepts to define, measure or explain. Their presentation and the experiences of them are subjective and vary from one person to the next. Improving the management of MO will require that this complexity be acknowledged and allowed to guide us through more interdisciplinary inquiry if there are to be more effective solutions for people suffering from MO.

Finally, this thesis shows how considerably MO diminishes HRQOL. Gauteng residents suffering from MO are potentially unaware of their diagnosis and therefore of potential management for their disorder. Awareness around MO needs to be the first step in limiting this disorder's devastating impact on individuals, their relationships and their potential to contribute meaningfully to society.

References

- 1000 Genomes. (2012). *A deep catalog of human genetic variation*. Retrieved from www.1000genomes.org
- Abbate-Daga, G., Fassino, S., Lo Giudice, R., Rainero, I., Gramaglia, C., Marech, L., Pinessi, L. (2007). Anger, depression and personality dimensions in patients with migraine without aura. *Psychotherapy and Psychosomatics*, 76(2), 122–128.
- AbDSerotec. (2015). An Introduction to ELISA: What is ELISA, procedures, types of ELISA, detection options and results. Retrieved from <https://www.bio-rad-antibodies.com/an-introduction-to-elisa.html>
- Abnova. (n.d.). *Glutamate ELISA Kit*. Abnova.
- Abokrysha, N. (2009). Ibn Sina (Avicenna) on Pathogenesis of migraine compared with the recent theories. *Headache*, 49(6), 923–928.
- Abu Bakar, N., Tanprawate, S., Lambro, G., Torkamani, M., Jahanshahi, M., & Matharu, M. (2016). Quality of life in primary headache disorders : A review. *Cephalalgia*, 36(1), 67–91. doi:10.1177/0333102415580099
- Abu-Saad Huijjer, H., Abboud, S. Predictors of quality of life in a sample of Lebanese patients with cancer. *Europe's Journal of Psychology*, 9(1), 8-18.
- Ad Hoc Committee on Classification of Headache. (1962). Classification of headache. *Journal of the American Medical Association*, 179(9), 127–128.
- Addington-Hall, J., & Kalra, L. (2001). Who should measure quality of life? *BMJ (Clinical Research Ed.)*, 322(7299), 1417–20. <http://doi.org/doi:10.1136/bmj.322.7299.1417>
- Adoukonou, T., Houinato, D., & Kankouan, J. (2009). Migraine Among University Students in Cotonou (Benin). *Headache*, 49, 887–893. doi:10.1111/j.1526-4610.2009.01408.x
- Aegidius, K. L., Zwart, J., Hagen, K., Schei, B., & Stovner, L. J. (2007). Hormone replacement

- therapy and headache prevalence in postmenopausal women. The Head-HUNT study. *European Journal of Neurology : The Official Journal of the European Federation of Neurological Societies*, 14(1), 73–8. <http://doi.org/10.1111/j.1468-1331.2006.01557.x>
- Agostini, E., & Aliprandi, A. (2008). Migraine and hypertension. *Neurological Sciences*, 29(S1), 37–39.
- Aguggia, M. (2012). Allodynia and migraine. *Neurological Sciences*, 33(Supplement 1), S9–11. doi:10.1007/s10072-012-1034-9
- Alam, Z., Coombes, N., Waring, R., Williams, A., & Steventon, G. (1998). Plasma levels of neuroexcitatory amino acids in patients with migraine or tension headache. *Journal of Neurological Sciences*, 156(1), 102–106.
- Alexander, L. (2014). *History of Headache*. In Headache Australia. Retrieved from <http://headacheaustralia.org.au/what-is-headache/history-of-headache/>
- Aliprandi, A., Longoni, M., Stanzani, L., Tremolizzo, L., Vaccaro, M., Begni, B., Ferrarese, C. (2005). Increased plasma glutamate in stroke patients might be linked to altered platelet release and uptake. *Journal of Cerebral Blood Flow and Metabolism*, 25(4), 513–519. doi:10.1038/sj.jcbfm.9600039
- Amiel, J. M., & Mathew, S. J. (2007). Glutamate and anxiety disorders. *Current Psychiatry Reports*, 9(4), 278–283. doi:10.1007/s11920-007-0033-7
- Andrasik, F. (2006). Psychophysiological disorders: Headache as a case in point. In *Comprehensive handbook of personality and psychopathology: Vol. 2: Adult Psychopathology*. (pp. 409–422). Hoboken: John Wiley & Sons Inc.

- Andrasik, F., Buse, D. C., & Grazzi, L. (2009). Behavioral medicine for migraine and medication overuse headache. *Current Pain and Headache Reports*, *13*(3), 241–8. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/19457287>
- Andrasik, F., Flor, H., & Turk, D. C. (2005). An expanded view of psychological aspects in head pain: the biopsychosocial model. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *26*(2), s87–91. doi:10.1007/s10072-005-0416-7
- Andreou, A. P., & Goadsby, P. J. (2011). Topiramate in the treatment of migraine: a kainate (glutamate) receptor antagonist within the trigeminothalamic pathway. *Cephalalgia : An International Journal of Headache*, *31*(13), 1343–58. doi:10.1177/0333102411418259
- Androutsos, Dimos-dimitrios Mitsikostas, G., Tulp, N., Willis, T., Swieten, G. Van, Ceasar, J., Paul, S., & Jefferson, T. (2009). *Headaches in antiquity and during the early scientific era*, 1215–1220. doi:10.1007/s00415-009-5085-7
- Anttila, V., Stefansson, H., Kallela, M., Todt, U., Terwindt, G. M., Calafato, M. S., ... Palotie, A. (2010). Genome-wide association study of migraine implicates a common susceptibility variant on 8q22.1. *Nature Genetics*, *42*(10), 869–73. doi:10.1038/ng.652
- Ashing-Giwa, K. T., Tejero, J., Kim, J., Padilla, G., & Hellemann, G. (2007). Examining predictive models of HRQOL in a population-based, multiethnic sample of women with breast carcinoma. *Quality of Life Research*, *16*(3), 413–428. <http://doi.org/10.1007/s>
- Au, A., Li, P., Chan, J., Lui, C., Ng, P., Kwok, A., & Leung, P. (2002). Predicting the quality of life in Hong Kong Chinese adults with epilepsy. *Epilepsy & Behavior*, *3*(4), 350–357. doi:10.1016/S1525-5050(02)00034-3

- Autret, A., Roux, S., Rimbaux-Lepage, S., Valade, D., & Debiais, S. (2010). Psychopathology and quality of life burden in chronic daily headache: influence of migraine symptoms. *The Journal of Headache and Pain*, *11*(3), 247–253. doi:10.1007/s10194-010-0208-1
- Aydemir, N., Özkara, Ç., Ünsal, P., & Canbeyli, R. (2011). A comparative study of health related quality of life, psychological well-being, impact of illness and stigma in epilepsy and migraine. *Seizure*, *20*(9), 679–685. doi:10.1016/j.seizure.2011.06.017
- Bak, L. K., Schousboe, A., & Waagepetersen, H. S. (2006). The glutamate/GABA-glutamine cycle: aspects of transport, neurotransmitter homeostasis and ammonia transfer. *Journal of Neurochemistry*, *98*(3), 641–653. doi:10.1111/j.1471-4159.2006.03913.x
- Bakas, T., McLennon, S. M., Carpenter, J. S., Buelow, J. M., Otte, J. L., Hanna, K. M., ... Welch, J. L. (2012). Systematic review of health-related quality of life models. *Health & Quality of Life Outcomes*, *10*(1), 134–145. doi:10.1186/1477-7525-10-134
- Baron, E. P., & Tepper, S. J. (2010). Revisiting the Role of Ergots in the Treatment of Migraine. *Headache*, *50*(8), 1353–1361. doi:10.1111/j.1526-4610.2010.01662.x
- Barsdorf, N. W., & Wassenaar, D. R. (2005). Racial differences in public perceptions of voluntariness of medical research participants in South Africa. *Social Science & Medicine*, *60*, 1087–1098. <http://doi.org/10.1016/j.socscimed.2004.06.039>
- Becker, M., Diamond, R., & Sainfort, F. (2011). A new patient focused index for measuring quality of life in persons with severe and persistent mental illness. *Quality of Life Research*, *2*(4), 239–251.
- Behar, K. L., & Rothman, D. L. (2001). Glutamine Metabolism : Nutritional and Clinical Significance In Vivo Nuclear Magnetic Resonance Studies of Glutamate- -Aminobutyric

Acid-Glutamine Cycling in Rodent and Human Cortex: the Central Role of Glutamine
Cycling in Rodent and Huma. *Journal of Nutrition*, 131, 2498S–2504S.

Ben-Arye, E., Bar-Sela, G., Frenkel, G., Kuten, A., & Hermoni, D. (2006). Is a Biopsychosocial
– Spiritual Approach Relevant to Cancer Treatment ? A Study of Patients and Oncology
Staff Members on Issues of Complementary Medicine and Spirituality Is a biopsychosocial
– spiritual approach relevant to cancer treatment ? A study o. *Support Care Cancer*,
14(147–152). <http://doi.org/10.1007/s00520-005-0866-8>

Benedict, R. H. B., Wahlig, E., Bakshi, R., Fishman, I., Munschauer, F., Zivadinov, R., &
Weinstock-Guttman, B. (2005). Predicting quality of life in multiple sclerosis: accounting
for physical disability, fatigue, cognition, mood disorder, personality, and behavior
change. *Journal of the Neurological Sciences*, 231(1-2), 29–34.
[doi:10.1016/j.jns.2004.12.009](https://doi.org/10.1016/j.jns.2004.12.009)

Bera, S., Goyal, V., Khandelwal, S., & Sood, M. (2014). A comparative study of psychiatric
comorbidity, quality of life and disability in patients with migraine and tension type
headache. *Neurology India*, 62(5), 516. [doi:10.4103/0028-3886.144445](https://doi.org/10.4103/0028-3886.144445)

Blau, J. N. (1984). Occasional review Migraine pathogenesis : the neural hypothesis reexamined.
Journal of Neurology, Neurosurgery, and Psychiatry, 47, 437–442.

Bleakman, D., Alt, A., & Nisenbaum, E. S. (2006). Glutamate receptors and pain. *Seminars in
Cell and Developmental Biology*, 17(5), 592–604. [doi:10.1016/j.semcdb.2006.10.008](https://doi.org/10.1016/j.semcdb.2006.10.008)

Bliese, P., & Halverson, R. R. (1998). Group Size and Measures of Group - Level Properties : An
Examination of Eta - Squared and ICC Values. *Journal of Management*, 24(2), 157–172.
[doi:10.1177/014920639802400202](https://doi.org/10.1177/014920639802400202)

- Blomkvist, V., Hannerz, J., Katz, L., & Theorell, T. (2001). Coping style and social support in men and women suffering from cluster headache or migraine. *Headache*, *42*, 178–184.
- Boes, C. J., & Capobianco, D. J. (2005). Chronic migraine and medication-overuse headache through the ages. *Cephalalgia : An International Journal of Headache*, *25*(5), 378–90. doi:10.1111/j.1468-2982.2005.00868.x
- Borrell-Carrió, F., Suchman, A., & Epstein, R. (2004). The Biopsychosocial Model 25 Years Later : *Annals of Family Medicine*, *2*(6), 576–582. doi:10.1370/afm.245
- Borsook, D., Maleki, N., Becerra, L., & McEwen, B. (2012). Understanding Migraine through the Lens of Maladaptive Stress Responses: A Model Disease of Allostatic Load. *Neuron*, *73*(2), 219–234. doi:10.1016/j.neuron.2012.01.001
- Bot, A., Becker, S., Bruijnzeel, H., Mulders, M., Ring, D., & Vranceanu, A. (2014). Creation of the Abbreviated Measures of the Pain Catastrophizing Scale and the Short Health Anxiety Inventory: The PCS-4 and SHAI-5. *Journal of Musculoskeletal Pain*, *22*(2), 145–151.
- Bourke, J. (2013). What is pain? A history. *Transactions of the Royal Historical Society*, *23*, 155–173.
- Bowling, A. (2001). *Measuring disease* (2nd ed.). Philadelphia: Open University Press. doi:10.1001/jama.1994.03520080061045
- Boyles, D. R. (2006). Dewey's Epistemology: an Argument for Warranted Assertions, Knowing, and Meaningful Classroom Practice. *Educational Theory*, *56*(1), 57–68. doi:10.1111/j.1741-5446.2006.00003.x
- Boz, C., Velioglu, S., Ozmenoglu, M., Sayar, K., Alioglu, Z., Yalman, B., & Topbas, M. (2004). Temperament and character profiles of patients with tension-type headache and migraine.

- Psychiatry and Clinical Neurosciences*, 58(5), 536–43. doi:10.1111/j.1440-1819.2004.01297.x
- Bozzani, F. M., Alavi, Y., Jofre-Bonet, M., & Kuper, H. (2012). A comparison of the sensitivity of EQ-5D, SF-6D and TTO utility values to changes in vision and perceived visual function in patients with primary open-angle glaucoma. *BMC Ophthalmology*, 12(1), 43. doi:10.1186/1471-2415-12-43
- Branch, M. (2009). Headache disability in orofacial pain patients is related to traumatic life events. *Headache*, 49(4), 535–40. doi:10.1111/j.1526-4610.2008.01182.x
- Brazier, J., Roberts, J., & Deverill, M. (2002). The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics*, 21(2), 271–292.
- Breslau, N., & Davis, G. (1993). Migraine, physical health and psychiatric disorder: a prospective epidemiologic study in young adults. *Journal of Psychiatric Research*, 27(2), 211–221. Retrieved from <http://www.sciencedirect.com/science/article/pii/002239569390009Q>
- Brna, P., Gordon, K., & Dooley, J. (2006). Health-related quality of life among Canadians with migraine. *Journal of Headache and Pain*, 8, 43–48. doi:10.1007/s10194-007-0320-4
- Brna, P., Gordon, K., & Dooley, J. (2008). Canadian adolescents with migraine: impaired health-related quality of life. *Journal of Child Neurology*, 23(1), 39–43. doi:10.1177/0883073807307987
- Broman, J., Hassel, B., Rinvik, E., & Ottersen, O. P. (2000). Chapter 1 Biochemistry and anatomy of transmitter glutamate. *Handbook of Chemical Neuroanatomy*, 18, 1–44. doi:10.1016/S0924-8196(00)80042-1
- Broome, J. (1995). Qalys. *Journal of Public Economics*, 50(2), 149–167. doi:10.1016/0047

- Brown, I., & Brown, R. (2003). Quality of life: A model for practice. *Quality of Life and Disability: An Approach for Community Practitioners*, 98–121.
- Brown, J. S., Neumann, P. J., Papadopoulos, G., Ruoff, G., Diamond, M., & Menzin, J. (2008). Migraine frequency and health utilities: Findings from a multisite survey. *Value in Health*, 11(2), 315–321. doi:10.1111/j.1524-4733.2007.00246.x
- Brown, J. S., Neumann, P. J., Papadopoulos, G., Ruoff, G., Diamond, M., & Menzin, J. (2008). Migraine frequency and health utilities: Findings from a multisite survey. *Value in Health*, 11(2), 315–321. doi:10.1111/j.1524-4733.2007.00246.x
- Brown, J. S., Papadopoulos, G., Neumann, P. J., Friedman, M., Miller, J. D., & Menzin, J. (2005). Cost-Effectiveness of Topiramate in Migraine Prevention : Results From a Pharmacoeconomic Model of Topiramate Treatment. *Headache*, 45(8), 1012–1022.
- Brown, J., Bowling, A & Flynn, T. N. (2004). *Models of Quality of Life*. A taxonomy and systematic review of the literature.
- Brown, R. I., & Brown, I. (2005). The application of quality of life. *Journal of Intellectual Disability Research*, 49(10), 718–727. doi:10.1111/j.1365-2788.2005.00740.x
- Busija, D. W., Bari, F., Domoki, F., Horiguchi, T., & Shimizu, K. (2008). Mechanisms involved in the cerebrovascular dilator effects of cortical spreading depression. *Progress in Neurobiology*, 86(4), 417–433. doi:10.1016/j.pneurobio.2008.09.008
- Bustin, S. A., Benes, V., Garson, J. A., Hellemans, J., Huggett, J., Kubista, M., Shipley, G. L. (2009). The MIQE Guidelines : Minimum Information for Publication of Quantitative Real-Time PCR Experiments, *Clinical Chemistry*, 55(4), 611-622.
doi:10.1373/clinchem.2008.112797
- Butali, A., Mossey, P., Tiffin, N., Adeyemo, W., Eshete, M., Mumena, C., ... Adeyemo, A.

- (2015). Multidisciplinary approach to genomics research in Africa: the AfriCRAN model. *PanAfrican Medical Journal*, 21, 229–232. <http://doi.org/10.11604/pamj.2015.21.229.7380>
- Butler, J. E. (2008). Enzyme-linked immunosorbent assay. *Journal of Immunoassay*, 21(2-3), 165–209. doi:10.1080/01971520009349533
- Cage, J. (2013). Postmodernism, Neuroscience and the Brain. *Proceedings of Singapore Healthcare*, 22(3), 158–162.
- Calati, R., Giegling, I., Rujescu, D., Hartmann, A. M., Möller, H.-J., De Ronchi, D., & Serretti, A. (2008). Temperament and character of suicide attempters. *Journal of Psychiatric Research*, 42(11), 938–45. <http://doi.org/10.1016/j.jpsychires.2007.10.006>
- Callaghan, P. (1998). Social support and locus of control as correlates of UK nurses' health-related behaviours. *Journal of Advanced Nursing*, 28(5), 1127–33. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9840886>
- Cananzi, A., D'Andrea, G., Perini, F., Zamberlan, F., & Welch, K. (1995). Platelet and plasma levels of glutamate and glutamine in migraine with and without aura. *Cephalalgia*, 15(2), 132–135.
- Caproni, S., Bianchi, E., Cupini, L. M., Corbelli, I., Beghi, E., & Calabresi, P. (2015). Migraine-specific quality of life questionnaire and relapse of medication overuse headache. *BMC Neurology*, 1–5. <http://doi.org/10.1186/s12883-015-0339-8>
- Cargan, L. (2007). *Doing Social research*. Maryland: Rowamn & Littlefield Publisher's, Inc.
- Carod-Artal, F. J., Stieven Trizotto, D., Ferreira Coral, L., & Menezes Moreira, C. (2009). Determinants of quality of life in Brazilian stroke survivors. *Journal of the Neurological Sciences*, 284(1-2), 63–68. doi:10.1016/j.jns.2009.04.008

- Cater, R. J., Vandenberg, R. J., & Ryan, R. M. (2014). The Domain Interface of the Human Glutamate Transporter EAAT1 Mediates Chloride Permeation. *Biophysical Journal*, *107*(3), 621–629. doi:10.1016/j.bpj.2014.05.046
- Cecchin, G. (1987). Hypothesizing, circularity, and neutrality revisited: an invitation to curiosity. *Family Process*, *26*(4), 405–13. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/3319683>
- Celikel, F. C., Kose, S., Cumurcu, B. E., Erkorkmaz, U., Sayar, K., Borckardt, J. J., & Cloninger, C. R. (2009). Cloninger's temperament and character dimensions of personality in patients with major depressive disorder. *Comprehensive Psychiatry*, *50*(6), 556–61. doi:10.1016/j.comppsy.2008.11.012
- Cella, D. F. (1994). Quality of life: concepts and definition. *Journal of Pain and Symptom Management*, *9*(3), 186–92. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/8014530>
- Centers for Disease Control and Prevention. (2011). HRQOL Concepts. *Hrqol*. Retrieved from <http://www.cdc.gov/hrqol/concept.htm>
- Chan, R., Brooks, R., Steel, Z., Heung, T., Erlich, J., Chow, J., & Suranyi, M. (2012). The psychosocial correlates of quality of life in the dialysis population: a systematic review and meta-regression analysis. *Quality of Life Research*, *21*(4), 563–580. doi:10.1007/s11136-011-9973-9
- Chanen, A. M., Jackson, H. J., Mccutcheon, L. K., Jovev, M., Dudgeon, P., Yuen, H. P., & Germano, D. (2008). Early intervention for adolescents with borderline personality disorder using cognitive analytic therapy : randomised controlled trial. *The British Journal of Psychiatry*, *6*, 477–484. <http://doi.org/10.1192/bjp.bp.107.048934>

- Chang, L. (2004). Review article: epidemiology and quality of life in functional gastrointestinal disorders. *Alimentary Pharmacology & Therapeutics*, *20 Suppl 7*, 31–9.
doi:10.1111/j.1365-2036.2004.02183.x
- Chapman, C. R., Tuckett, R. P., & Song, C. W. (2008). Pain and stress in a systems perspective: Reciprocal neural, endocrine, and immune interactions. *The Journal of Pain*, *9*(2), 122–145. doi:10.1016/j.jpain.2007.09.006
- Chapman, G. (2000). Glutamate and Glutamine in the Brain Glutamate and Epilepsy. *The Journal of Nutrition*, *130*(4), 1043S–1045S.
- Charan, S., & Gautam, O. (1984). Applications of Enzyme-linked immunosorbent assay in veterinary medicine: A bibliography. *Veterinary Research Communications*, *8*, 255–267.
- Charles, A., & Brennan, K. (2009). Cortical spreading depression-new insights and persistent questions. *Cephalalgia*, *29*(10), 1115–1124. doi:10.1111/j.1468-2982.2009.01983.x
- Chasman, D. I., Schürks, M., Anttila, V., de Vries, B., Schminke, U., Launer, L. J., Kurth, T. (2011). Genome-wide association study reveals three susceptibility loci for common migraine in the general population. *Nature Genetics*, *43*(7), 695–698.
doi:10.1017/CBO9781107415324.004
- Chess, S., & Thomas, A. (1996). *Temperament: Theory and practice*. New York: Brunner/Mazel, Inc.
- Chia, Y., Lim, S., & Wang, S. (2003). Efficacy of Eletriptan in Migraineurs With Persistent Poor Response to Nonsteroidal Anti-inflammatory Drugs. *Headache*, *43*, 984–991.
- Chiros, C., & O'Brien, W. H. (2011). Acceptance, appraisals, and coping in relation to migraine headache: an evaluation of interrelationships using daily diary methods. *Journal of Behavioral Medicine*, *34*(4), 307–20. doi:10.1007/s10865-011-9313-0

- Cho, S., Kim, H.-Y., & Lee, J.-H. (2012). Validation of the Korean version of the Pain Catastrophizing Scale in patients with chronic non-cancer pain. *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*. doi:10.1007/s11136-012-0308-2
- Christensen, A. F., Le, H., Kirchmann, M., & Olesen, J. (2012). Genotype-phenotype correlation in migraine without aura focusing on the rs1835740 variant on 8q22.1. *The Journal of Headache and Pain*, 13(1), 21–7. doi:10.1007/s10194-011-0386-5
- Classification Subcommittee of the International Headache Society. (2005). The International Classification of Headache Disorders: 2nd edition. *Neurologia I Neurochirurgia Polska*, 40(2 Suppl 1), S7–41.
- Cloninger, C. R., Zohar, A. H., Hirschmann, S., & Dahan, D. (2012). The psychological costs and benefits of being highly persistent: personality profiles distinguish mood disorders from anxiety disorders. *Journal of Affective Disorders*, 136(3), 758–66.
<http://doi.org/10.1016/j.jad.2011.09.046>
- Coelho, F. M. S., Pradella-Hallinan, M., Abud, P. C., Predazzoli Neto, M., Moreira, F., Bittencourt, L. R. A., Tufik, S. (2007). Prevalence of HLA DQB1*0602 allele in patients with migraine. *Arquivos de Neuro-Psiquiatria*, 65(4B), 1123–5. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/18345414>
- Cohen, J. (1992). A power primer. *Psychological Bulletin*, 112, 155-159. doi:10.1037/0033-2909.112.1.155
- Cohen, A., & Koenig, H. (2003). Religion, religiosity and spirituality in the biopsychosocial model of health and ageing. *Ageing International*, 28(3), 215–241.

- Cohen, L., Manion, L., & Morrison, K. (2005). *Research Methods in Education* (5th ed.). London and New York: Taylor & Francis e-library.
- Cohen, L., Manion, L., & Morrison, K. (2011). *Research Methods in Education* (7th ed.). New York: Routledge.
- Colman, S. S., Brod, M. I., Krishnamurthy, A., Rowland, C. R., Jirgens, K. J., & Gomez-Mantilla, B. (2000). Treatment Satisfaction, Functional Status, and Health-Related Quality of Life of Migraine Patients Treated with Almotriptan or Sumatriptan, *Clinical Therapeutics*, 23(1), 127–145.
- Colman, S. S., Brod, M. I., Krishnamurthy, A., Rowland, C. R., Jirgens, K. J., & Gomez-Mantilla, B. (2001). Treatment Satisfaction , Functional Status , and Health- Related Quality of Life of Migraine Patients Treated with Almotriptan or Sumatriptan. *Clinical Therapeutics*, 23(1), 127–145.
- Colson, N. J., Lea, R. A, Quinlan, S., MacMillan, J., & Griffiths, L. R. (2005). Investigation of hormone receptor genes in migraine. *Neurogenetics*, 6(1), 17–23. doi:10.1007/s10048-004-0205-0
- Compas, B. E., Connor-Smith, J., & Jaser, S. S. (2004). Temperament, stress reactivity, and coping: implications for depression in childhood and adolescence. *Journal of Clinical Child and Adolescent Psychology : The Official Journal for the Society of Clinical Child and Adolescent Psychology, American Psychological Association, Division 53*, 33(1), 21–31. doi:10.1207/S15374424JCCP3301_3
- Conrad, R., Schilling, G., Bausch, C., Nadstawek, J., Wartenberg, H. C., Wegener, I., Liedtke, R. (2007). Temperament and character personality profiles and personality disorders in chronic pain patients. *Pain*, 133(1-3), 197–209. doi:10.1016/j.pain.2007.07.024

- Copeman, J. (2009). *Veins of Devotion: Blood Donation and Religious Experience in North India*. Piscataway: Rutgers University Press.
- Coppola, G., Pierelli, F., & Schoenen, J. (2009). Habituation and migraine. *Neurobiology of Learning and Memory*, 92(2), 249–59. doi:10.1016/j.nlm.2008.07.006
- Cornish, D., Holterhues, C., van de Poll-Franse, L. V., Coebergh, J. W., & Nijsten, T. (2009). A systematic review of health-related quality of life in cutaneous melanoma. *Annals of Oncology : Official Journal of the European Society for Medical Oncology / ESMO*, 20 Suppl 6(SUPPL. 4), vi51–i58. doi:10.1093/annonc/mdp255
- Corr, P. J., & Perkins, A. M. (2006). The role of theory in the psychophysiology of personality: from Ivan Pavlov to Jeffrey Gray. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, 62(3), 367–76. doi:10.1016/j.ijpsycho.2006.01.005
- Creswell, J. W. (2003). A Framework for Design. In *Research design Qualitative quantitative and mixed methods approaches* (pp. 3–26). doi:10.3109/08941939.2012.723954
- Crowther, J. R. (2002). *The ELISA Guidebook*. Totowa, NJ: Humana Press.
- Cull-Candy, S. (2002). Ionotropic glutamate receptors: Functional and pharmacological properties in relation to constituent subunits. In J. Egebjerg, A. Schousboe, & P. Krogsgaard-Larsen (Eds.), *Glutamate and GABA Receptors and Transporters: Structure, Function and Pharmacology* (pp. 3–40). New York: Taylor & Francis.
- D’Amico, D., Grazi, L., Usai, S., Leonardi, M., & Raggi, A. (2013). Disability and quality of life in headache: where we are now and where we are heading? *Neurological Sciences*, 34(S1), 1–5. doi:10.1007/s10072-013-1378-9

- D'Amico, D., Leonardi, M., Grazi, L., Curone, M., & Raggi, A. (2015). Disability and quality of life in patients with different forms of migraine. *The Journal of Headache and Pain*, *16*(Suppl 1), 3–4. doi:10.1186/1129-2377-16-S1-A4
- D'Andrea, G., & Leon, a. (2010). Pathogenesis of migraine: from neurotransmitters to neuromodulators and beyond. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *31 Suppl 1*, S1-7. <http://doi.org/10.1007/s10072-010-0267-8>
- Dalhof, C., & Dimenas, E. (1995). Migraine patients experience poorer subjective well-being/quality of life even between attacks. *Cephalalgia*, *15*(1), 31–36.
- Danbolt, N. C. (2001). Glutamate uptake. *Progress in Neurobiology*, *65*(1), 1–105. doi:10.1016/S0301-0082(00)00067-8
- Davies, K., Macfarlane, G. J., McBeth, J., Morriss, R., & Dickens, C. (2009). Insecure attachment style is associated with chronic widespread pain. *Pain*, *143*(3), 200–5. doi:10.1016/j.pain.2009.02.013
- Davies, P. (2011). What has imaging taught us about migraine? *Maturitas*, *70*(1), 34–6. doi:10.1016/j.maturitas.2011.06.008
- Davison, K. P., Pennebaker, J. W., & Dickerson, S. S. (2000). Who talks? The social psychology of illness support groups. *The American Psychologist*, *55*(2), 205–217. <http://doi.org/10.1037/0003-066X.55.2.205>
- De Benedittis, G., Lorenzetti, A., & Pieri, A. (1990). The role of stressful life events in the onset of chronic primary headache. *Pain*, *40*(1), 65–75.
- De Filippis, S., Erbuto, D., Gentili, F., Innamorati, M., Lester, D., Tatarelli, R., Pompili, M. (2008). Mental turmoil, suicide risk, illness perception, and temperament, and their

- impact on quality of life in chronic daily headache. *The Journal of Headache and Pain*, 9(6), 349–57. doi:10.1007/s10194-008-0072-4
- Dean, B., Gerner, D., & Gerner, H. (2004). A systematic review evaluating health -related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder -. *Current Medical Research and Opinion*, 20(2), 139–154.
- Dean, C. E. (2011). Psychopharmacology: a house divided. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 35(1), 1–10.
<http://doi.org/10.1016/j.pnpbp.2010.08.028>
- De Pauw, S. S. W., & Mervielde, I. (2010). Temperament, Personality and Developmental Psychopathology: A Review Based on the Conceptual Dimensions Underlying Childhood Traits. *Child Psychiatry and Human Development*, 313–329. doi:10.1007/s10578-009-0171-8
- De Velasco, I. R., & Gonzalez, N. (2003). Quality of life in migraine patients: a qualitative study. *Cephalalgia*, 23(9), 892–900. Retrieved from
<http://onlinelibrary.wiley.com/doi/10.1046/j.1468-2982.2003.00599.x/full>
- Dean, B., Gerner, D., & Gerner, H. (2004). A systematic review evaluating health-related quality of life, work impairment, and healthcare costs and utilization in bipolar disorder -. *Current Medical Research and Opinion*, 20(2), 139–154.
- Dean, C. E. (2011). Psychopharmacology: a house divided. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 35(1), 1–10.
doi:10.1016/j.pnpbp.2010.08.028
- Dell, S. (2010). South Africa: Decline in PhD numbers a major problem. Retrieved March 30, 2016, from

<http://www.universityworldnews.com/article.php?story=20100820150736361&mode=print>

Deshmukh, V. D. (2006). Retino-hypothalamic-pineal hypothesis in the pathophysiology of primary headaches. *Medical Hypotheses*, 66(6), 1146–51.

doi:10.1016/j.mehy.2005.12.026

Dewey, J. (1905). The Realism of Pragmatism. *Journal of Philosophy*, 2(12), 324–327.

Di Piero, V., Bruti, G., Venturi, P., Talamonti, F., Biondi, M., Di Legge, S., & Lenzi, G. L.

(2001). Aminergic tone correlates of migraine and tension-type headache: a study using the tridimensional personality questionnaire. *Headache*, 41(1), 63–71. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11168605>

Diego, et al. (2004). Recognition and management of migraine in primary care : influence of functional impact measured by the headache impact test (HIT). *Cephalalgia*, 25, 184–190. doi:10.1111/j.1468-2982.2004.00820.x

Diener, H. C., Steiner, T. J., & Tepper, S. J. (2006). Migraine - The forgotten epidemic:

Development of the EHF/WHA Rome Declaration on migraine. *Journal of Headache and Pain*, 7(6), 433–437. <http://doi.org/10.1007/s10194-006-0349-4>

Domingos, P. (1999). The role of Occam’s razor in knowledge discovery. *Data Mining and Knowledge Discovery*, 425, 409–425.

Downing, N., Williams, J., Leserman, A., & Paulsen, J. (2013). Couples’ Coping in Prodromal Huntington Disease: A Mixed Methods Study. *Journal of Genetic Counselling*, 21(5), 662–670. doi:10.1007/s10897-012-9480-3.Couples

Dyer, J. (2003). Multidisciplinary, interdisciplinary, and transdisciplinary Educational models and nursing education. *Nursing Education Perspectives*, 24(4), 186–188.

- Eadie, M. J. (2003). An 18th century understanding of migraine – Samuel Tissot (1728-1797).
Journal of Clinical Neuroscience, 10(4), 414–419. doi:10.1016/S0967-5868(03)00067-5
- Eadie, M. J. (2005). The pathogenesis of migraine – 17th to early 20th Century understandings.
Journal of Clinical Neuroscience, 12(4), 383–388. doi:10.1016/j.jocn.2004.12.003
- Eadie, M. J. (2012). A history of migraine. In D. Borsook, A. May, P.J.Goadsby, R. Hargreaves.
(Eds.), *The migraine brain: Imaging structure and function* (pp. 3–16). New York:
Oxford University Press.
- Eck, J., Richter, M., Straube, T., Miltner, W. H. R., & Weiss, T. (2011). Affective brain regions
are activated during the processing of pain-related words in migraine patients. *Pain*,
152(5), 1104–1113. doi:10.1016/j.pain.2011.01.026
- Eikermann-Haerter, K., Kudo, C., & Moskowitz, M. a. (2007). Cortical spreading depression and
estrogen. *Headache*, 47 Suppl 2, S79–85. doi:10.1111/j.1526-4610.2007.00818.x
- Elliot, R. H. (1932). Migraine and Mysticism. *Postgraduate Medical Journal*, 8(86), 449–459.
- Elliott, J. O., & Richardson, V. (2014). The biopsychosocial model and quality of life in persons
with active epilepsy. *Epilepsy & Behavior*, 41, 55–65. doi:10.1016/j.yebeh.2014.09.035
- Engel, G. (1977). The Need for a New Medical Model : A Challenge for Biomedicine. *Science*,
196(4286), 129–136.
- Engel, G. L. (1980). The clinical application of the biopsychosocial model. *The American
Journal of Psychiatry*, 137(5), 535–544. doi:10.1176/ajp.137.5.535
- Engvall, E., & Perlmann, P. Enzyme linked immunosorbent assay (ELISA). Quantitative assay
of immunoglobulin G. *Immunochemistry*, 8(9), 871-874.

- Esposito, M., Marotta, R., Gallai, B., Parisi, L., Patriciello, G., Lavano, S. M., Carotenuto, M. (2013). Temperamental characteristics in childhood migraine without aura: a multicenter study. *Neuropsychiatric Disease and Treatment*, 9, 1187–92. doi:10.2147/NDT.S50458
- Esposito, M., Marotta, R., Gallai, B., Parisi, L., Patriciello, G., Lavano, S. M., Di Dona, A. (2013). Attachment styles in children affected by migraine without aura. *Neuropsychiatric Disease and Treatment*, 9, 1513–1519.
- Esposito, M., Roccella, M., Gallai, B., Parisi, L., Lavano, S. M., Marotta, R., & Carotenuto, M. (2013). Maternal personality profile of children affected by migraine. *Neuropsychiatric Disease and Treatment*, 9, 1351–1358. doi:10.2147/NDT.S51554
- Facchinetti, F., Nappi, R., Tirelli, A., Polatti, F., & Nappi, G. (2002). Brief Communication Hormone Supplementation Differently Affects Migraine in Postmenopausal Women. *Headache: The Journal of Head and Face Pain*, 42, 924–929.
- Fadel, F. I., Elshamaa, M. F., Essam, R. G., Elghoroury, E. A., El-saeed, G. S. M., El-toukhy, S. E., & Ibrahim, M. H. (2014). Some Amino Acids Levels : Glutamine , Glutamate , and Homocysteine , in Plasma of Children with Chronic Kidney Disease, *10*(1), 36–42.
- Farah, M. J. (2005). Neuroethics: The practical and the philosophical. *Trends in Cognitive Sciences*, 9(1), 34–40. doi:10.1016/j.tics.2004.12.001
- Fasmer, O. B., Akiskal, H. S., Kelsoe, J. R., & Oedegaard, K. J. (2009). Clinical and Pathophysiological Relations Between Migraine and Mood Disorders. *Current Psychiatry Reviews*, 5(2), 93–109.
- Fernandes, L., Storheim, K., Lochting, I., & Grotle, M. (2012). Cross-cultural adaptation and validation of the Norwegian pain catastrophizing scale in patients with low back pain. *BMC Musculoskeletal Disorders*, 13, 111. doi:10.1186/1471-2474-13-111

- Ferraguti, F., & Shigemoto, R. (2006). Metabotropic glutamate receptors. *Cell and Tissue Research*, 326(2), 483–504. doi:10.1007/s00441-006-0266-5
- Ferrans, C. (2005). Definitions and conceptual models of quality of life . In J. Lipscomb, C. C. Gotay, & C. Snyder (Eds.), *Outcomes Assessment in Cancer: Measures, Methods and Applications* (pp. 14–30). Cambridge: Cambridge University Press.
- Ferrans, C. E., Zerwic, J. J., Wilbur, J. E., & Larson, J. L. (2005). Conceptual Model of Health-Related Quality of Life. *Journal of Nursing Scholarship*, 37(4), 336–342.
doi:10.1111/j.1547-5069.2005.00058.x
- Ferrari, A., Spaccapelo, L., Pinetti, D., Tacchi, R., & Bertolini, A. (2009). Effective prophylactic treatments of migraine lower plasma glutamate levels. *Cephalalgia*, 29(4), 423–429.
<http://doi.org/10.1111/j.1468-2982.2008.01749.x>
- Ferrari, M., Odink, J., Bos, K., Malessy, M., & Bruyn, G. (1990). Neuroexcitatory plasma amino acids are elevated in migraine. *Neurology*, 40(10), 1582–1586.
- Field, A. (2000). Discovering statistics using SPSS for Windows: advanced techniques for the beginner. In *Research Methods I: SPSS for windows* (pp. 1–9). London: Sage. Retrieved from Relationships Between Variables.
- Field, A. (2013). Linear Models : Looking for Bias More on Bias. Retrieved January 28, 2016, from www.statisticshell.com/docs/linearmodelsbias.pdf
- Finocchi, C., Villani, V., & Casucci, G. (2010). Therapeutic strategies in migraine patients with mood and anxiety disorders: clinical evidence. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, 31 Suppl 1, S95-8. <http://doi.org/10.1007/s10072-010-0297-2>

- Fischer, F. (1998). Beyond empiricism: policy inquiry in post positivist perspective. *Policy Studies Journal*, 26(1998), 129–146. doi:10.1111/j.1541-0072.1998.tb01929.x
- Floden, R. E. (2009). Empirical Research Without Certainty. *Educational Theory*, 59(4), 485–498. doi:10.1111/j.1741-5446.2009.00332.x
- Fowler, F. J. (2009). *Survey Research Methods* (4th ed.). Thousand Oaks: SAGE Publications.
- Fox, N. J. (2008). Post-positivism. In L. M. Given (Ed.), *The SAGE Encyclopaedia of Qualitative Research Methods* (pp. 659–664). SAGE.
- Foxhall, K. (2014). Making modern migraine medieval: men of science, Hildegard of Bingen and the life of a retrospective diagnosis. *Medical History*, 58(3), 354–74.
doi:10.1017/mdh.2014.28
- Fraga, D., Meulia, T., & Fenster, S. (2008). Real-Time PCR. In S. Gallagher & A. Wiley (Eds.), *Current Protocols Essential Laboratory Techniques* (pp. 10.3.1–10.3.33). Online Library: John Wiley & Sons Inc.
- Freitag, F. G. (2007). The Cycle of Migraine : Patients' Quality of Life During and Between Migraine Attacks, 29(5), 939–949.
- Freilinger, T., Anttila, V., Vries, B. De, & Malik, R. (2013). Genome-wide association analysis identifies susceptibility loci for migraine without aura. *Nature Genetics*, 44(7), 777–782.
doi:10.1038/ng.2307.Genome-wide.
- Friedman, A. P. (1968). The migraine syndrome. *Bulletin of the New York Academy of Medicine*, 44(1), 45–62.
- Fuh, J., & Wang, S. (2006). Comparison of the Short Form-36 and Migraine Disability Assessment questionnaire in patients with migraine. *Clinical Journal of Pain*, 22(6), 564–568.

- Fuller-Thomson, E., Baker, T. M., & Brennenstuhl, S. (2010). Investigating the Association Between Childhood Physical Abuse and Migraine. *Headache: The Journal of Head and Face Pain*, 50(5), 749–760. doi:10.1111/j.1526-4610.2010.01626.x
- Galletti, F., Cupini, L. M., Corbelli, I., Calabresi, P., & Sarchielli, P. (2009). Pathophysiological basis of migraine prophylaxis. *Progress in Neurobiology*, 89(2), 176–92. doi:10.1016/j.pneurobio.2009.07.005
- Gajovic, S. (2015). Publishing interdisciplinary research – a perspective from the Croatian Medical Journal. *Croatian Medical Journal*, 56, 399–400. <http://doi.org/10.1038/525306a>
- Gana, K., & Trouillet, R. (2003). Structure invariance of the Temperament and Character Inventory (TCI). *Personality and Individual Differences*, 35(7), 1483–1495. [http://doi.org/10.1016/S0191-8869\(02\)00364-1](http://doi.org/10.1016/S0191-8869(02)00364-1)
- Gatchel, Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological Bulletin*, 133(4), 581–624. doi:10.1037/0033-2909.133.4.581
- Gatchel, R. (2004). Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. *The American Psychologist*, 59(8), 795–805. doi:10.1037/0003-066X.59.8.795
- Gatchel, R. J., & Turk, D. C. (2008). Criticisms of the biopsychosocial model in spine care: creating and then attacking a straw person. *Spine*, 33(25), 2831–6. doi:10.1097/BRS.0b013e31817d24ad
- Gatchel, R., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: scientific advances and future directions. *Psychological Bulletin*, 133(4), 581–624. doi:10.1037/0033-2909.133.4.581

- Gentzler, A. L., Kerns, K., & Keener, E. (2009). Emotional reactions and regulatory responses to negative and positive events: Associations with attachment and gender. *Motivation and Emotion*, 34(1), 78–92. doi:10.1007/s11031-009-9149-x
- George, S. Z., Wallace, M. R., Wright, T. W., Moser, M. W., Greenfield, W. H., Sack, B. K., ... Fillingim, R. B. (2008). Evidence for a biopsychosocial influence on shoulder pain: pain catastrophizing and catechol-O-methyltransferase (COMT) diplotype predict clinical pain ratings. *Pain*, 136(1-2), 53–61. doi:10.1016/j.pain.2007.06.019
- Gerth, W. C., Carides, G. W., Dasbach, E. J., Visser, W. H., & Santanello, N. C. (2001). The multinational impact of migraine symptoms on healthcare utilisation and work loss. *Pharmacoeconomics*, 19(2), 197–206. doi:10.2165/00019053-200119020-00006
- Geweke, L. (2006). Wolff ' s Headache and Other Head Pain. *Archives of Neurology*, 66(4), 537. doi:10.1001/archneurol.2009.17.Text
- Ghaemi, S. N. (2009). *The rise and fall of the biopsychosocial model: reconciling art and science in psychiatry*. Maryland: The Johns Hopkins University Press. Retrieved from <http://journals.psychiatryonline.org/article.aspx?articleid=102397>
- Gillespie, N., Cloninger, C. R., Heath, A. C., & Martin, N. G. (2003). The genetic and environmental relationship between Cloninger's dimensions of temperament and character. *Personality and Individual Differences*, 35(8), 1931–1946. doi:10.1016/S0191-8869(03)00042-4
- Goadsby, P. J. (2007). Recent advances in understanding migraine mechanisms, molecules and therapeutics. *Trends in Molecular Medicine*, 13(1), 39–44. doi:10.1016/j.molmed.2006.11.005

- Goadsby, P., Ferrari, M. D., Csanyi, A., Olesen, J., & Mills, J. G. (2009). Randomized, double-blind, placebo-controlled, proof-of-concept study of the cortical spreading depression inhibiting agent tonabersat in migraine prophylaxis. *Cephalalgia: An International Journal of Headache*, 29(7), 742–750. doi:10.1111/j.1468-2982.2008.01804.x
- Goode, D. (1994). Towards an understanding of holistic quality of life in people with profound intellectual and multiple disabilities. In D. Goode (Ed.), *Quality of life for persons with disabilities: International perspectives and issues*. (pp. 197–207). Cambridge: Brookline Books. doi:10.1017/CBO9781107415324.004
- Granziera, C., Daducci, A., Romascano, D., Roche, A., Helms, G., Krueger, G., & Hadjikhani, N. (2014). Structural abnormalities in the thalamus of migraineurs with aura: A multiparametric study at 3 T. *Human Brain Mapping*, 35, 1461–1468. doi:10.1002/hbm.22266
- Green, A. (2015). Effective treatment for the queen of brain-pains remains a headache. Retrieved February 15, 2016, from <http://mg.co.za/article/2015-09-04-effective-treatment-for-the-queen-of-brain-pains-remains-a-headache>
- Gurwitz, D., & Diamond, S. (2007). Prioritizing Migraine Biomarkers Research. *Drug Development Research*, 269, 267–269. doi:10.1002/ddr
- Gybels, J., Handwerker, H., & Van Hees, J. (1979). A comparison between the discharges of human nociceptive nerve fibres and the subject's rating of his sensations. *Journal of Physiology*, 292, 193–206.
- H3Africa Working Group. (2013). *H3Africa Funding Informed Consent*. Retrieved from [http://www.health.uct.ac.za/sites/default/files/image_tool/images/116/H3Africa Guidelines on Informed Consent August 2013.pdf](http://www.health.uct.ac.za/sites/default/files/image_tool/images/116/H3Africa%20Guidelines%20on%20Informed%20Consent%20August%202013.pdf)

- Haas, D. C. (1996). Chronic post-traumatic headaches classified and compared with natural headaches. *Cephalalgia*, *16*(7), 486–493. <http://doi.org/10.1046/j.1468-2982.1996.1607486.x>
- Hachaturova, M. (2010). The Role of Personality Traits in Choosing of Coping Strategies in an Organizational Conflict. *World Academy of Science, Engineering & Technol*, *66*, 1347–1348.
- Hamed, S. (2009). The vascular risk associations with migraine: Relation to migraine susceptibility and progression. *Atherosclerosis*, *205*, 15–22.
[doi:10.1016/j.atherosclerosis.2008.10.016](http://doi.org/10.1016/j.atherosclerosis.2008.10.016)
- Hamel, E. (2006). Perivascular nerves and the regulation of cerebrovascular tone. *Journal of Applied Physiology*, *100*(3), 1059–1064.
- Hanmer, J., Lawrence, W. F., Anderson, J. P., Kaplan, R. M., & Fryback, D. G. (2006). Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. *Medical Decision Making : An International Journal of the Society for Medical Decision Making*, *26*(4), 391–400.
<http://doi.org/10.1177/0272989X06290497>
- Hansenne, M., Reggers, J., Pinto, E., Kjiri, K., Ajamier, A., & Ansseau, M. (1999). Temperament and character inventory (TCI) and depression. *Journal of Psychiatric Research*, *33*(1), 31–6. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10094237>
- Hartley, C., & Slater, R. (2014). Neurophysiological measures of nociceptive brain activity in the newborn infant - the next steps. *Acta Paediatrica, International Journal of Paediatrics*, *103*, 238–242. [doi:10.1111/apa.12490](http://doi.org/10.1111/apa.12490)

- Hashimoto, K., Sawa, A., & Iyo, M. (2007). Increased Levels of Glutamate in Brains from Patients with Mood Disorders. *Biological Psychiatry*, 62(11), 1310–1316.
doi:10.1016/j.biopsych.2007.03.017
- Hashizume, M., Yamada, U., Sato, A., Hayashi, K., Amano, Y., Makino, M., Tsuboi, K. (2008). Stress and psychological factors before a migraine attack: a time-based analysis. *BioPsychoSocial Medicine*, 2, 14. doi:10.1186/1751-0759-2-14
- Hayes, A. F. (2013). *Introduction to mediation, moderation, and conditional process analysis: A regression-based approach*. New York: Guilford Press.
- Hazard, E., Munakata, J., Bigal, M. E., Rupnow, M. F. T., & Lipton, R. B. (2009). The Burden of Migraine in the United States: Current and Emerging Perspectives on Disease Management and Economic Analysis. *Value in Health*, 12(1), 55–64. doi:10.1111/j.1524-4733.2008.00404.x
- Headache Classification Committee of the International Headache Society. (2005). The International Classification of Headache Disorders: 2nd edition. *Neurologia I Neurochirurgia Polska*, 40(2 Suppl 1), S7–41. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20816417>
- Headache Classification Committee of the International Headache Society. (1988). Classification (Vol. 49, pp. 6–8). doi:10.3109/00016485809124430
- Headache Classification Committee of the International Headache Society. (2013). The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia: An International Journal of Headache*, 33(9), 629–808.
doi:10.1177/0333102413485658

- Headache Classification Subcommittee of the International Headache Society. (2004). The International Classification of Headache Disorders 2nd Edition ICHD-II. *Headache*, 48(5), 691–3. doi:10.1111/j.1526-4610.2008.01121.x
- Headache Classification Committee of the International Headache Society. (2005). The International Classification of Headache Disorders: 2nd edition. *Neurologia I Neurochirurgia Polska*, 40(2 Suppl 1), S7–41. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/20816417>
- Henderson, H., & Wachs, T. D. (2007). Temperament theory and the study of cognition–emotion interactions across development. *Developmental Review*, 27(3), 396–427. doi:10.1016/j.dr.2007.06.004
- Heresco-Levy, U., Bar, G., Levin, R., Ermilov, M., Ebstein, R. P., & Javitt, D. C. (2007). High glycine levels are associated with prepulse inhibition deficits in chronic schizophrenia patients. *Schizophrenia Research*, 91(1-3), 14–21. doi:10.1016/j.schres.2006.12.003
- Herrera Ponce, M. S., Barros Lezaeta, C., & Fernández Lorca, M. B. (2011). Predictors of Quality of Life in Old Age: A Multivariate Study in Chile. *Journal of Population Ageing*, 4, 121–139. doi:10.1007/s12062-011-9043-7
- Hertz, L. (2013). The Glutamate–Glutamine (GABA) Cycle: Importance of Late Postnatal Development and Potential Reciprocal Interactions between Biosynthesis and Degradation. *Frontiers in Endocrinology*, 4(May), 1–16. doi:10.3389/fendo.2013.00059
- Higginson, I., & Carr, A. (2001). Using quality of life measures in the clinical setting. *Bmj*, 322, 1297–1300. doi:10.1136/bmj.322.7297.1297

- Hitt, H. C., McMillen, R. C., Thornton-Neaves, T., Koch, K., & Cosby, A. G. (2007). Comorbidity of Obesity and Pain in a General Population: Results from the Southern Pain Prevalence Study. *Journal of Pain*, 8(5), 430–436. doi:10.1016/j.jpain.2006.12.003
- Hjermstad, M. J., Fayers, P. M., Haugen, D. F., Caraceni, A., Hanks, G. W., Loge, J. H., ... Kaasa, S. (2011). Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: A systematic literature review. *Journal of Pain and Symptom Management*, 41(6), 1073–1093. doi:10.1016/j.jpainsymman.2010.08.016
- Ho, W. W. N., Chiu, M. Y. L., Lo, W. T. L., & Yiu, M. G. C. (2010). Recovery components as determinants of the health-related quality of life among patients with schizophrenia: structural equation modelling analysis. *Australian and New Zealand Journal of Psychiatry*, 44(1), 71–84. doi:10.3109/00048670903393654
- Holm, P., Holst, J., & Perlt, B. (1994). Co-write your own life: Quality of life as discussed in the Danish Context. In *Quality of life for persons with disabilities: International perspectives and issues*. (pp. 1–21). Cambridge: Brookline Books. doi:10.1017/CBO9781107415324.004
- Holroyd, K., Drew, J., Cottrell, C., Romanek, K., & Heh, V. (2007). Impaired functioning and quality of life in severe migraine: the role of catastrophizing and associated symptoms. *Cephalalgia*, 27(10), 1156–1165.
- Hong, C. J., Yu, Y. W., Lin, C. H., Cheng, C. Y., & Tsai, S. J. (2001). Association analysis for NMDA receptor subunit 2B (GRIN2B) genetic variants and psychopathology and clozapine response in schizophrenia. *Psychiatric Genetics*, 11(4), 219–222. doi:10.1097/00041444-200112000-00007

- Houinato, D., Adoukonou, T., Ntsiba, F., Adjien, C., Avode, D.-G., & Preux, P.-M. (2010). Prevalence of migraine in a rural community in south Benin. *Cephalalgia : An International Journal of Headache*, 30(1), 62–7. doi:10.1111/j.1468-2982.2009.01894.x
- Howel, D. C. (2013). Statistical methods for psychology. Belmont: Wadsworth. Retrieved from <https://www.uvm.edu/~dhowell/methods8/>
- Hung, C., Wang, S., Yang, C., & Liu, C. (2008). The impacts of migraine , anxiety disorders , and chronic depression on quality of life in psychiatric outpatients with major depressive disorder, 65, 135–142. <http://doi.org/10.1016/j.jpsychores.2008.04.011>
- Hwang, S. S., Chang, V. T., & Kasimis, B. (2002). Dynamic Cancer Pain Management Outcomes : The Relationship Between Pain Severity, Pain Relief, Functional Interference, Satisfaction and Global Quality of Life Over Time, *Journal of Pain and Symptom Management*, 23(3), 190–200.
- International Headache Society. (2004). The International Classification of Headache Disorders. *Headache*, 24(Supplement 1). doi:10.1111/j.1526-4610.2008.01121.x
- Irwin, M. (2008). Human psychoneuroimmunology: 20 years of discovery. *Brain, Behavior, and Immunity*, 22(2), 129–39. doi:10.1016/j.bbi.2007.07.013
- Jackson, T., Wang, Y., & Fan, H. (2014). Associations Between Pain Appraisals and Pain Outcomes: Meta-Analyses of Laboratory Pain and Chronic Pain Literatures. *The Journal of Pain : Official Journal of the American Pain Society*, 15(6), 586–601. <http://doi.org/10.1016/j.jpain.2014.01.499>
- Jacob, C. P., Koutsilieria, E., Bartla, J., Neuen-Jacobb, E., Arzbergere, T., Zandera, N., ... Grunblatt, E. (2007). Alterations in expression of glutamatergic transporters and receptors in sporadic Alzheimer’s disease . *Journal of Alzheimer’s Disease*, 11, 97–116.

- James, M. F., Smith, J. M., Boniface, S. J., Huang, C. L., & Leslie, R. A. (2001). Cortical spreading depression and migraine : new insights from imaging? *Trends in Neuroscience*, 24(5), 823–826.
- James, W. (1981). What pragmatism means. In *Pragmatism: A new name for some old ways of thinking* (pp. 43–81). Cambridge: University Printing House.
- Jensen, M., Chen, C., & Brugger, A. (2003). Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *The Journal of Pain*, 4(7), 407–414.
- Jette, N., Patten, S., & Williams, J. (2008). Comorbidity of Migraine and Psychiatric Disorders—A National Population Based Study. *Headache: The Journal of Head and Face Pain*, 48(4), 501–516. doi:10.1111/j.1526-4610.2007.00993.x
- Kanai, Y., & Hediger, M. A. (2003). The glutamate and neutral amino acid transporter family: Physiological and pharmacological implications. *European Journal of Pharmacology*, 479(1-3), 237–247. doi:10.1016/j.ejphar.2003.08.073
- Katsarava, Z., & Andre, C. (2011). The cost of headache disorders in Europe : the Eurolight project, 1–12. <http://doi.org/10.1111/j.1468-1331.2011.03612.x>
- Keating, C. L., Peeters, A., Swinburn, B. A., Magliano, D. J., & Moodie, M. L. (2012). Utility-Based Quality of Life Associated With Overweight and Obesity: The Australian Diabetes, Obesity, and Lifestyle Study. *Obesity*, 21(3), 652–655. doi:10.1038/oby.2012.151
- Kelley-Gillespie, N. (2009). An Integrated Conceptual Model of Quality of Life for Older Adults Based on a Synthesis of the Literature. *Applied Research in Quality of Life*, 4(3), 259–282. doi:10.1007/s11482-009-9075-9

- Kennedy, S. (2014). Troubleshooting RNA Isolation. Retrieved March 16, 2016, from <http://bitesizebio.com/2345/troubleshooting-rna-isolation/>
- Kenzik, K., Huang, I.-C., Rizzo, J. D., Shenkman, E., & Wingard, J. (2015). Relationships among symptoms, psychosocial factors, and health-related quality of life in hematopoietic stem cell transplant survivors. *Supportive Care in Cancer*, *23*(3), 797–807. doi:10.1007/s00520-014-2420-z
- Kerce, E. W. (1992). *Quality of Life: Meaning, Measurement, and Models*. Washington, DC.
- Kerns, R. D., Kassirer, M., & Otis, J. (2002). Pain in multiple sclerosis: a biopsychosocial perspective. *Journal of Rehabilitation Research and Development*, *39*(2), 225–32. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12051466>
- Kershaw, T. S., Ph, D., Mood, D. W., Sanda, M. G., Vaishampayan, U., Northouse, L. L., ... Ronis, D. L. (2008). Longitudinal analysis of a model to predict quality of life in prostate cancer patients and their spouses. *Ann Behav Med*, *36*(2), 117–128. doi:10.1007/s12160-008-9058-3
- Khanna, D., Furst, D., Wong, W., Tsevat, J., Clements, P., Park, G., Groups, S. C. T. 1 S. (2007). Reliability, validity, and minimally important differences of the SF-6D in systemic sclerosis. *Quality of Life Research*, *16*(6), 1083–1092.
- Kitamura, T., Kijima, N., Watanabe, K., Takezaki, Y., & Tanaka, E. (1999). Precedents of perceived social support: personality and early life experiences. *Psychiatry and Clinical Neurosciences*, *53*(6), 649–54. doi:10.1046/j.1440-1819.1999.00620.x
- Kjøgx, H., Kasch, H., Zachariae, R., Svensson, P., Jensen, T., & Vase, L. (2016). Experimental manipulations of pain catastrophizing influence pain levels in chronic pain patients and healthy volunteers. *Paediatrics and Child Health*.

<http://doi.org/10.1097/j.pain.0000000000000519>

- Kline, R. B. (2011). *Principles and Practice of Structural Equation Modeling: Third Edition*, 2011.
- Koehler, P. J., & Boes, C. J. (2010). A history of non-drug treatment in headache, particularly migraine. *Brain*, *133*, 2489–2500. doi:10.1093/brain/awq170
- Koehler, P., & Isler, H. (2002). The early use of ergotamine in migraine. Edward Woakes ' report of 1868, its theoretical and practical background and its international reception. *Cephalalgia*, *22*(8), 686–691. doi:10.1046/j.1468-2982.2002.00422.x
- Kolotylo, C. J., & Broome, M. E. (2000). Predicting disability and quality of life in a community-based sample of women with migraine headache. *Pain Management Nursing*, *1*(4), 139–151. doi:10.1053/jpmn.2000.19344
- Koyama, T., McHaffie, J. G., Laurienti, P. J., & Coghill, R. C. (2005). The subjective experience of pain: where expectations become reality. *Proceedings of the National Academy of Sciences of the United States of America*, *102*, 12950–12955. doi:10.1073/pnas.0408576102
- Kröner-Herwig, B., Morris, L., & Heinrich, M. (2008). Biopsychosocial correlates of headache: what predicts pediatric headache occurrence? *Headache*, *48*(4), 529–44. doi:10.1111/j.1526-4610.2007.00945.x
- Kruithof, W., van Mierlo, M., Visser-Meily, J., van Heugten, C., & Post, M. (2013). Associations between social support and stroke survivors' health-related quality of life - a systematic review. *Patient Education and Counseling*, *93*(2), 16176.

- Krystal, J. H., Sanacora, G., Blumberg, H., Anand, a, Charney, D. S., Marek, G., Mason, G. F. (2002). Glutamate and GABA systems as targets for novel antidepressant and mood-stabilizing treatments. *Molecular Psychiatry*, 7(s1), S71–S80. doi:10.1038/sj.mp.4001021
- Kuehn, M., & McClainm, J. (1994). Quality of life in the United States: A multicultural context. In D. Goode (Ed.), *Quality of life for persons with disabilities: International perspectives and issues*. (pp. 185–207). Cambridge: Brookline Books.
- l-t-b.org. (2009). Lifting The Burden. Retrieved March 31, 2016, from <http://www.l-t-b.org/>
- Lake, A. (2009). Headache as a Stressor : Dysfunctional versus Adaptive Coping Styles. *Headache: The Journal of Head and Face Pain*, 49(9), 1369–1378.
- Lampl, C., Buzath, A., Klinger, D., & Neumann, K. (1999). Lamotrigine in the prophylactic treatment of migraine aura—a pilot study. *Cephalalgia*, 19(1), 58–63. Retrieved from <http://onlinelibrary.wiley.com/doi/10.1111/j.1468-2982.1999.1901058.x/abstract>
- Lane, R., & Davies, P. (2006). *Migraine (Neurological disease and therapy)*. New York: Taylor & Francis.
- Lantéri-Minet, M., Auray, J.-P., El Hasnaoui, A., Dartigues, J.-F., Duru, G., Henry, P., ... Gaudin, A.-F. (2003). Prevalence and description of chronic daily headache in the general population in France. *Pain*, 102(1-2), 143–149. Retrieved from <http://www.sciencedirect.com/science/article/pii/S0304395902003482>
- Lantéri-Minet, M., Massiou, H., Nachit-Ouinekh, F., Lucas, C., Pradalier, A., Radat, F., El Hasnaoui, A. (2007). The GRIM2005 study of migraine consultation in France I. Determinants of consultation for migraine headache in France. *Cephalalgia : An International Journal of Headache*, 27(12), 1386–97. doi:10.1111/j.1468-2982.2007.01426.x

- Lantéri-Minet, M., Radat, F., Chautard, M., & Lucas, C. (2005). Anxiety and depression associated with migraine: Influence on migraine subjects' disability and quality of life, and acute migraine management. *Pain, 118*, 319–326. doi:10.1016/j.pain.2005.09.010
- Lasch, K., Greenhill, A., Wilkes, G., Carr, D., Lee, M., & Blanchard, R. (2002). Nursing Faculty and Students' Knowledge of and Attitudes to Cancer Pain Management, 5(1).
- Latham, P. (1872). On sick-headache. *British Medical Journal, 672*, 7–8. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2297087/>
- Leão, A. (1944). Spreading depression of activity cortex. *American Physiological Society, 7*(6), 359–390.
- Lee, M., & Tracey, I. (2013). Neuro-genetics of persistent pain. *Current Opinion in Neurobiology, 23*(1), 127–32. doi:10.1016/j.conb.2012.11.007
- Leonardi, M., Raggi, A., Bussone, G., & D'Amico, D. (2010). Health-Related Quality of Life, Disability and Severity of Disease in Patients With Migraine Attending to a Specialty Headache Center. *Headache: The Journal of Head and Face Pain, 50*, 1576–1587. doi:10.1111/j.1526-4610.2010.01770.x
- Leonardi, M., Steiner, T., Scher, A., & Lipton, R. (2005). The global burden of migraine: measuring disability in headache disorders with WHO's Classification of Functioning, Disability and Health (ICF). *The Journal of Headache and Pain, 6*(6), 429–440.
- Lequin, R. M. (2005). Enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay (ELISA). *Clinical Chemistry, 51*(12), 2415–2418. doi:10.1373/clinchem.2005.051532
- Lewis, B. (2008). The Biopsychosocial Model and Philosophic Pragmatism: Is George Engel a Pragmatist? *Philosophy, Psychiatry, & Psychology, 14*(4), 299–310. doi:10.1353/ppp.0.0142

- Ligthart, L., de Vries, B., Smith, A. V, Ikram, M. A., Amin, N., Hottenga, J.-J., Boomsma, D. I. (2011). Meta-analysis of genome-wide association for migraine in six population-based European cohorts. *European Journal of Human Genetics : EJHG*, 19(8), 901–7. doi:10.1038/ejhg.2011.48
- Linde, M. (2006). Migraine: a review and future directions for treatment. *Acta Neurologica Scandinavica*, 114(2), 71–83. doi:10.1111/j.1600-0404.2006.00670.x
- Ling, D., & Salvaterra, P. M. (2011). Robust RT-qPCR Data Normalization: Validation and Selection of Internal Reference Genes during Post-Experimental Data Analysis, 6(3). doi:10.1371/journal.pone.0017762
- Lipid Laboratory Johns Hopkins. (2003). *Laboratory Procedures Manual: Triglycerides , and LDL-Cholesterol*. Baltimore: Centers for Disease Control.
- Lipton, R., & Bigal, M. (2005). The epidemiology of migraine. *American Journal of Medicine Supplement*, 118, 3–10. doi:10.1016/j.amjmed.2005.01.014
- Lipton, R. B., Bigal, M. E., Kolodner, K., Stewart, W. F., Liberman, J. N., & Steiner, T. J. (2003). The family impact of migraine: population-based studies in the USA and UK. *Cephalalgia : An International Journal of Headache*, 23(6), 429–40. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12807522>
- Lipton, R., & Bigal, M. (2005). The epidemiology of migraine. *American Journal of Medicine Supplement*, 118, 3–10. <http://doi.org/10.1016/j.amjmed.2005.01.014>
- Lipton, R., Buse, D., Hall, C., Tennen, H., DeFreitas, T., Borkowski, T., Haut, S. (2014). Stress and migraine: Something expected, something unexpected. *Neurology*, 82(16), 1395–1401. doi:10.1212/WNL.0000000000000349

- Lipton, R., Hamelsky, S., Kolodner, K., Steiner, T., & Stewart, W. (2000). Migraine, quality of life, and depression: A population-based case-control study. *Neurology*, *55*(5), 629–635.
- Liszka, J. (2012). Pragmatism. In *Encyclopedia of Applied Ethics* (2nd ed., pp. 561–568). Elsevier.
- Livak, K. J., & Schmittgen, T. D. (2001). Analysis of Relative Gene Expression Data Using Real-Time Quantitative PCR and the $2^{-\Delta\Delta C_T}$ Method. *Methods*, *408*, 402–408.
doi:10.1006/meth.2001.1262
- Livinge, E. (1872). Observations on megrim or sick-headache. *British Medical Journal*, *588*, 364–366. doi:10.1136/bmj.1.588.364-a
- Loder, E., Harrington, M. G., Cutrer, M., Sandor, P., & De Vries, B. (2006). Selected confirmed, probable, and exploratory migraine biomarkers. *Headache*, *46*(7), 1108–27.
doi:10.1111/j.1526-4610.2006.00525.x
- Long, D. (2013). Pragmatism, realism, and psychology: Understanding theory selection criteria. *Journal of Contextual Behavioral Science*, *2*(3-4), 61–67.
- Longoni, M., & Ferrarese, C. (2006). Inflammation and excitotoxicity: role in migraine pathogenesis. *Neurological Sciences*, *27 Suppl 2*, S107–10. doi:10.1007/s10072-006-0582-2
- Longworth, L., & Bryan, S. (2003). An empirical comparison of EQ-5D and SF-6D in liver transplant patients. *Health Economics*, *12*(12), 1061–1067. <http://doi.org/10.1002/hec.787>
- Lowenthal, K. (2001). *An introduction to psychological tests and scales* (2nd ed.). Taylor & Francis.

- Lucas, C., Geraud, G., Valade, D., Chautad, M., & Lanteri-Minet, M. (2006). Recognition and therapeutic management of migraine in 2004, in France: Results of the FRAMIG 3, a French nationwide population-based survey. *Headache*, *46*(5), 715–725.
- Luciano, J., Andersson, B., Batchelor, C., Bodenreider, O., Clark, T., Denney, C., Dumontier, M. (2011). Translational Medicine Ontology and Knowledge Base driving personalized medicine by bridging the gap between bench and bedside. *Journal of Biomedical Semantics*, *17*(2 Supplement 2), S1.
- Ludvigsson, P., Hesdorffer, D., Olafsson, E., Kjartansson, O., & Hauser, W. A. (2006). Migraine with aura is a risk factor for unprovoked seizures in children. *Annals of Neurology*, *59*(1), 210–213. doi:10.1002/ana.20745
- Lumley, M., Cohen, J. L., Borszcz, G. S., Cano, A., Radcliffe, A. M., Porter, L. S., Keefe, F. J. (2011). Pain and emotion: a biopsychosocial review of recent research. *Journal of Clinical Psychology*, *67*(9), 942–68. doi:10.1002/jclp.20816
- Lundblad, R. L. (2008). Considerations for the Use of Blood Plasma and Serum for Proteomic Analysis, *1*(2), 1–19.
- Luoni, C., Bisulli, F., Canevini, M. P., De Sarro, G., Fattore, C., Galimberti, C. A., Perucca, E. (2011). Determinants of health-related quality of life in pharmaco-resistant epilepsy: Results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. *Epilepsia*, *52*(12), 2181–2191. doi:10.1111/j.1528-1167.2011.03325.x
- Lutgendorf, S., & Costanzo, E. (2003). Psychoneuroimmunology and health psychology: An integrative model. *Brain, Behavior, and Immunity*, *17*, 225–232. doi:10.1016/S0889-1591(03)00033-3

- Magee, L. (2011). PAXgene Blood RNA Tubes. *TechTalk*, 8(11), 4–5.
- Magnusson, J. E., & Becker, W. J. (2003). Migraine frequency and intensity: relationship with disability and psychological factors. *Headache*, 43(10), 1049–59. doi:10.1046/j.1526-4610.2003.03206.x
- Mallolas, J., Hurtado, O., Castellanos, M., Blanco, M., Sobrino, T., Serena, J., Dávalos, A. (2006). A polymorphism in the EAAT2 promoter is associated with higher glutamate concentrations and higher frequency of progressing stroke. *The Journal of Experimental Medicine*, 203(3), 711–7. doi:10.1084/jem.20051979
- Malt, E.A. & Ursin, H. (2003). Mutilation anxiety differs among females with fibromyalgia and functional dyspepsia and population controls. *Journal of Psychosomatic Research*, 54(6), 523-531.
- Mangina, C. (2009). Historical milestones of neuroscientific psychophysiology. *International Journal of Psychophysiology : Official Journal of the International Organization of Psychophysiology*, 73(2), 76–80. doi:10.1016/j.ijpsycho.2009.04.008
- Mao, J. (2009). Translational pain research: achievements and challenges. *Journal of Pain*, 10(10), 1001–1011.
- Marais, A., & Stuart, A. (2006). The role of temperament in the development of Post-traumatic Stress Disorder amongst journalists. *South African Journal of Psychology*, 35(1), 89–105.
- Mardaga, S., & Hansenne, M. (2007). Relationships between Cloninger’s biosocial model of personality and the behavioral inhibition/approach systems (BIS/BAS). *Personality and Individual Differences*, 42(4), 715–722. doi:10.1016/j.paid.2006.08.013
- Marks, N. F. (2010). Psychological Effects of Childhood Violence, 84(1), 1–17.
<http://doi.org/10.1086/652786.Sense>

- Martin, B. C., Pathak, D. S., Sharfman, M. I., Adelman, J. U., Taylor, F., Kwong, W. J., & Jhingran, P. (2000). Validity and reliability of the migraine-specific quality of life questionnaire (MSQ Version 2.1). *Headache*, *40*(3), 204–15. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10759923>
- Martin, P. (2008). Psychological assessment and the treatment of chronic headache. *InPsych*, *38*(4). Retrieved from <https://www.psychology.org.au/inpsych/2016/#Aug2016>
- Martin, P. R. (2007). Headaches Should be Conceptualized Within the Framework of the Biopsychosocial Model. *Headache*, *47*(1), 137. doi:10.1111/j.1526-4610.2007.00662_2.x
- Martin, P., & Soon, K. (1993). The relationship between perceived stress, social support and chronic headaches. *Headache*, *33*(6), 307–314.
- Martisova, E., Solas, M., Horrillo, I., Ortega, J. E., Meana, J. J., Tordera, R. M., & Ramírez, M. J. (2012). Long lasting effects of early-life stress on glutamatergic/GABAergic circuitry in the rat hippocampus. *Neuropharmacology*, *62*(5-6), 1944–53. doi:10.1016/j.neuropharm.2011.12.019
- Materazzo, F., Cathcart, S., & Pritchard, D. (2000). Anger, depression, and coping interactions in headache activity and adjustment: a controlled study. *Journal of Psychosomatic Research*, *49*(1), 69–75.
- Mathew, N. T. (2001). Pathophysiology, epidemiology, and impact of migraine. *Clin Cornerstone*, *4*(3), 1–17. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12739312>
- Matsumoto, Y., Suzuki, A., Ishii, G., Oshino, S., Otani, K., & Goto, K. (2007). The -181 A/C polymorphism in the excitatory amino acid transporter-2 gene promoter affects the personality trait of reward dependence in healthy subjects. *Neuroscience Letters*, *427*(2), 99–102. doi:10.1016/j.neulet.2007.09.015

- Mayosi, B. M., Flisher, A. J., Lalloo, U. G., Sitas, F., Tollman, S. M., Bradshaw, D., ... Africa, S. (2009). Health in South Africa 4 The burden of non-communicable diseases in South Africa, *6736(9)*, 1–14. [http://doi.org/10.1016/S0140-6736\(09\)61087-4](http://doi.org/10.1016/S0140-6736(09)61087-4)
- Mazzone, L., Vitiello, B., Incorpora, G., & Mazzone, D. (2006). Behavioural and temperamental characteristics of children and adolescents suffering from primary headache. *Cephalalgia*, *26(8)*, 194–201. doi:10.1111/j.1468-2982.2005.01015.x
- Mccall, M. N., McMurray, H., Land, H., & Almudevar, A. (2014). Non-detects in qPCR data : methods to model and impute non-detects in the results of qPCR experiments (non-detects). *Bioinformatics*, *30(16)*, 2310–2316.
- McCracken, L. (1998). Learning to live with the pain : Acceptance of pain predicts adjustment in persons with chronic pain . *Pain*, *74*, 21–27. doi:10.1016/S0304-3959(97)00146-2
- McEwen, B. (2012). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences*, *109(Supplement_2)*, 17180–17185. doi:10.1073/pnas.1121254109
- McEwen, B., Elland, L., Hunter, R., & Miller, M. (2012). Stress and anxiety: Structural plasticity and epigenetic regulation As a Consequence of Stress. *Neuropharmacology*, *62(1)*, 3–12. doi:10.1016/j.neuropharm.2011.07.014.Stress
- McGeeney, B. E. (2009). An introduction to headache classification. *Techniques in Regional Anesthesia and Pain Management*, *13(1)*, 2–4. doi:10.1053/j.trap.2009.03.007
- McHugh, P. R. (1992). A structure for psychoatry at the century's turn - the view from Johns Hopkins. *Journal of the Royal Society of Medicine*, *85(August)*, 483–487.
- McKelvey, B. (2001). Foundations of “ New ” Social Science: Institutional Legitimacy from Philosophy, Complexity Science, Postmodernism and Agent-based Modeling. In *Sackler*

Colloquium on Agents, Intelligence, and Emergent Human Organization: Capturing Complexity Through Agent-Based Modeling.

- McLaren, N. (1998). A critical review of the biopsychosocial model. *Australasian Psychiatry*, 32(1), 86–92; discussion 93–6.
- Meldrum, B. S. (2000). Glutamate as a neurotransmitter in the brain: review of physiology and pathology. *The Journal of Nutrition*, 130(4S Suppl), 1007S–15S.
- Menezes, G. B., Mansur, D. S., McDonald, B., Kubes, P., & Teixeira, M. M. (2011). Sensing sterile injury: opportunities for pharmacological control. *Pharmacology & Therapeutics*, 132(2), 204–14. doi:10.1016/j.pharmthera.2011.07.002
- Mengistu, G., & Alemayehu, S. (2013). Prevalence and burden of primary headache disorders among a local community in Addis Ababa, Ethiopia. *The Journal of Headache and Pain*, 14(1), 30. doi:10.1186/1129-2377-14-30
- Mertens, J., Flisher, A., Ward, C., Bresick, G., Sterling, S., & Weisner, C. (2010). Medical conditions of hazardous drinkers and drug users in primary care clinics in Cape Town, South Africa. *Journal of Drug Issues*, 39(4), 1–26.
- Miguel-Hidalgo, J. J., Waltzer, R., Whittom, A. a, Austin, M. C., Rajkowska, G., & Stockmeier, C. (2010). Glial and glutamatergic markers in depression, alcoholism, and their comorbidity. *Journal of Affective Disorders*, 127(1-3), 230–40. doi:10.1016/j.jad.2010.06.003
- Milner, P. M. (1958). Electroencephalography and Clinical Neurophysiology Note on a possible correspondence between the scotomas of migraine and spreading depression of Leão. *Electroencephalography and Clinical Neurophysiology*, 10(4), 705. doi:10.1016/0013

- Molecular Diagnostic Laboratory. (2010). Documentation for NormFinder. Retrieved March 18, 2016, from [http://moma.dk/files/Normfinder documentation-v20.pdf](http://moma.dk/files/Normfinder%20documentation-v20.pdf)
- Mongini, F., Fassino, S., Rota, E., Deregibus, A., Levi, M., Monticone, D., & Abbate-Daga, G. (2005). The temperament and character inventory in women with migraine. *The Journal of Headache Pain*, 6, 247–249. doi:10.1007/s10194-005-0198-6
- Mongini, F., Keller, R., Deregibus, A., Barbalonga, E., & Mongini, T. (2005). Frontal lobe dysfunction in patients with chronic migraine : a clinical-neuropsychological study. *Psychiatry Research*, 133, 101–106. doi:10.1016/j.psychres.2003.12.028
- Mongini, F., Keller, R., Deregibus, A., Raviola, F., Mongini, T., & Sancarlo, M. (2003). Personality traits, depression and migraine in women: A longitudinal study. *Cephalalgia*, 23, 186–193.
- Mongini, F., Rota, E., Evangelista, A., Ciccone, G., Milani, C., Ugolini, A., Rosato, R. (2009). Personality profiles and subjective perception of pain in head pain patients. *Pain*, 144(1-2), 125–9. doi:10.1016/j.pain.2009.03.026
- Montagna, P. (2008). The primary headaches : genetics , epigenetics and a behavioural genetic model. *Journal of Headache and Pain*, 9, 57–69. doi:10.1007/s10194-008-0026-x
- Montazeri, A., Vahdaninia, M., Mousavi, S. J., Asadi-Lari, M., Omidvari, S., & Tavousi, M. (2011). The 12-item medical outcomes study short form health survey version 2.0 (SF-12v2): a population-based validation study from Tehran, Iran. *Health and Quality of Life Outcomes*, 9, 12. doi:10.1186/1477-7525-9-12
- Monteiro, A. P. T. D. A. V. (2011). Psychometric properties of a Russian version of the Social Support Questionnaire (SSQ6) in eastern European immigrants. *Contemporary Nurse*, 39(2), 157–62. doi:10.5172/conu.2011.157

- Montoya, P., Larbig, W., Braun, C., Preissl, H., & Birbaumer, N. (2004). Influence of social support and emotional context on pain processing and magnetic brain responses in fibromyalgia. *Arthritis and Rheumatism*, *50*(12), 4035–4044.
<http://doi.org/10.1002/art.20660>
- Montoya, P., Pauli, P., Batra, A., & Wiedemann, G. (2005). Altered processing of pain-related information in patients with fibromyalgia. *European Journal of Pain (London, England)*, *9*(3), 293–303. <http://doi.org/10.1016/j.ejpain.2004.07.012>
- Moons, P. (2004). Why call it health-related quality of life when you mean perceived health status? *European Journal of Cardiovascular Nursing*, *3*(4), 275–277.
[doi:10.1016/j.ejcnurse.2004.09.004](http://doi.org/10.1016/j.ejcnurse.2004.09.004)
- Morris, L. D., Grimmer-Somers, K. a, Louw, Q. a, & Sullivan, M. J. (2012). Cross-cultural adaptation and validation of the South African Pain Catastrophizing Scale (SA-PCS) among patients with fibromyalgia. *Health and Quality of Life Outcomes*, *10*(1), 137.
[doi:10.1186/1477-7525-10-137](http://doi.org/10.1186/1477-7525-10-137)
- Mula, M., Viana, M., Jauch, R., Schmitz, B., Bettucci, D., Cavanna, a E., Monaco, F. (2009). Health-related quality of life measures and psychiatric comorbidity in patients with migraine. *European Journal of Neurology : The Official Journal of the European Federation of Neurological Societies*, *16*(9), 1017–21. [doi:10.1111/j.1468-1331.2009.02636.x](http://doi.org/10.1111/j.1468-1331.2009.02636.x)
- Nagata, E., Hattori, H., Kato, M., Ogasawara, S., Suzuki, S., Shibata, M., ... Takagi, S. (2009). Identification of biomarkers associated with migraine with aura. *Neuroscience Research*, *64*(1), 104–10. [doi:10.1016/j.neures.2009.02.001](http://doi.org/10.1016/j.neures.2009.02.001)

- Najam, N., & Aslam, S. (2010). Perceived Stress and Coping Strategies in Headache (Migraine & Tension-Type Headache) Patients. *Journal of Behavioural Sciences*, 20, 1–15.
- Napolitano, T. (2008). *Psychosocial and disability differences between patients with migraine headaches with and without aura*. Walden University.
- National Headache Foundation. (2006). Poetry. Retrieved from <http://www.headaches.org/category/headache-support/headache-poetry/>
- National Research Foundation. (2014). New Centres of Excellence to advance interdisciplinary research. Retrieved March 30, 2016, from <http://mg.co.za/article/2014-06-26-new-centres-of-excellence-to-advance-interdisciplinary-research>
- Nestvold, K., & Stavem, K. (2009). Determinants of health-related quality of life 22 years after hospitalization for traumatic brain injury. *Brain Injury*, 23(1), 15–21.
doi:10.1080/02699050802530540
- Newton, R. (2008). Childhood chronic daily headache : a biopsychosocial perspective. *Developmental Medicine & Child Neurology*, 50, 484.
- Nicholson, R. A., Houle, T. T., Rhudy, J. L., Norton, P. J., & Forest, W. (2007). Psychological Risk Factors in Headache. *Headache*, 47, 413–426. doi:10.1111/j.1526-4610.2006.00716.x
- Nicholson, R. A., Hursey, K. G., & Nash, J. M. (2005). Focus on Behavioral Moderators and Mediators of Behavioral Treatment for Headache. *Headache*, 45, 513–519.
- Nickel, J. C., Tripp, D. a., Chuai, S., Litwin, M. S., McNaughton-Collins, M., Landis, J. R., ... Stevens, M. (2008). Psychosocial variables affect the quality of life of men diagnosed with chronic prostatitis/chronic pelvic pain syndrome. *BJU International*, 101(1), 59–64.
doi:10.1111/j.1464-410X.2007.07196.x

- Nigg, J. (2006). Temperament and developmental psychopathology. *Journal of Child Psychology and Psychiatry*, 47(3/4), 395–422. doi:10.1111/j.1469-7610.2006.01612.x
- NIH. (2012). *Human Subjects Protection and Inclusion of Women, Minorities, and Children Guidelines for Review of NIH Grant Applications Requirements for Review Requirements for Review*. NIH.
- Nolan, T., Hands, R. E., & Bustin, S. a. (2006). Quantification of mRNA using real-time RT-PCR. *Nature Protocols*, 1(3), 1559–82. doi:10.1038/nprot.2006.236
- Norton, P. J., Asmundson, G. J., Norton, G. R., & Craig, K. D. (1999). Growing pain: 10-year research trends in the study of chronic pain and headache. *Pain*, 79(1), 59–65.
- Nuamah, I. F., Cooley, M. E., Fawcett, J., & McCorkle, R. (1999). Testing a theory for health-related quality of life in cancer patients: a structural equation approach. *Research in Nursing & Health*, 22, 231–242.
- Nutt, D., & Lingford-Hughes, A. (2004). Key concepts in psychopharmacology. *Psychiatry*, 3(7), 1–4. doi:10.1383/psyt.3.7.1.42877
- Nyholt, D. R., LaForge, K. S., Kallela, M., Alakurtti, K., Anttila, V., Färkkilä, M., Palotie, A. (2008). A high-density association screen of 155 ion transport genes for involvement with common migraine. *Human Molecular Genetics*, 17(21), 3318–31. doi:10.1093/hmg/ddn227
- Nylander, P.-O., Schlette, P., Brandstrom, S., Nilsson, M., Forsgren, T., Forsgren, L., & Adolfsson, R. (1996). Migraine: Temperament and Character, 30(5), 359–368.
- Oliveira, P., Monteiro, P., Coutinho, M., Salvador, M. J., Costa, M. E., & Malcata, A. (2009). Qualidade de vida e vivencia da dor cronica nas doencas reumaticas. *Acta Reumatologia Portugal*, 34, 511–519.

- Ong, J. C., Gramling, S. E., Vrana, S. R., Nicholson, R. a., & Buenaver, L. F. (2006). Psychophysiological responses of female headache sufferers and controls using a picture-viewing paradigm. *Applied Psychophysiology and Biofeedback, 31*(4), 295–313. doi:10.1007/s10484-006-9026-2
- Optum. (n.d.). The SF-6D. Retrieved from <https://www.optum.com/content/dam/optum/resources/Manual Excerpts/SF-6D.pdf>
- Ordu Gokkaya, N. K., Gokce-Kutsal, Y., Borman, P., Ceceli, E., Dogan, A., Eyigor, S., & Karapolat, H. (2012). Pain and quality of life (QoL) in elderly: The Turkish experience. *Archives of Gerontology and Geriatrics, 55*(2), 357–362. doi:10.1016/j.archger.2011.10.019
- Osman, A., Barrios, F., Kopper, B., Hauptmann, W., Jones, J., & O’Neill, E. (1997). Factor structure, reliability, and validity of the Pain Catastrophizing Scale. *Journal of Behavioral Medicine, 20*(6), 589–605. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9429990>
- Ostberg, A.-L., & Hall-Lord, M.-L. (2011). Oral health-related quality of life in older Swedish people with pain problems. *Scandinavian Journal of Caring Sciences, 25*(3), 510–6. doi:10.1111/j.1471-6712.2010.00857.x
- Osterhaus, J. T., Gutterman, D. L., & Plachetka, J. R. (1992). Health Care Resource and Lost Labor Costs of Migraine Headache in the US. *Pharmacoeconomics, 2*(1), 67–76.
- Østhus, T. B. H., Preljevic, V. T., Sandvik, L., Leivestad, T., Nordhus, I. H., Dammen, T., & Os, I. (2012). Mortality and health-related quality of life in prevalent dialysis patients: Comparison between 12-items and 36-items short-form health survey. *Health and Quality of Life Outcomes, 10*, 46. doi:10.1186/1477-7525-10-46

- Osuntokun, B., Adeuja, A., Nottidge, V., Bademosi, O., Alumide, A., Ige, O., Bolis, C. (1992). Prevalence of headache and migrainous headache in Nigerian Africans: a community-based study. *East African Medical Journal*, *69*(4), 196–199.
- Pampliega, O., Domercq, M., Villoslada, P., & Sepulcre, J. (2008). Association of an EAAT2 polymorphism with higher glutamate concentration in relapsing multiple sclerosis. *Journal of Neuroimmunology*, *195*, 194–198. doi:10.1016/j.jneuroim.2008.01.011
- Párdutz, A., Fejes, A., Bohár, Z., Tar, L., Toldi, J., & Vécsei, L. (2012). Kynurenines and headache. *Journal of Neural Transmission (Vienna, Austria : 1996)*, *119*(2), 285–96. <http://doi.org/10.1007/s00702-011-0665-y>
- Park, J., Han, S., & Yang, D. (2006). Serotonin transporter protein polymorphism and harm avoidance personality in migraine without aura. *Headache: The Journal ...*, *46*, 991–996. <http://doi.org/10.1111/j.1526-4610.2006.00439.x>
- Parmenter, T. (1992). Quality of life of people with developmental disabilities. In N. Bray (Ed.), *International review of research in mental retardation* (Vol. 18, pp. 247–302). San Diego: Academic Press, Inc.
- Parmenter, T. R. (1994). Quality of life as a concept and measurable entity. *Social Indicators Research*, *33*(1-3), 9–46. doi:10.1007/BF01078957
- Parry, O., Gnich, W., & Platt, S. (2001). Principles in practice: reflections on a “postpositivist” approach to evaluation research. *Health Education Research*, *16*(2), 215–26. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11345663>
- Parsons, A. A., & Strijbos, P. J. L. M. (2003). The neuronal versus vascular hypothesis of migraine and cortical spreading depression. *Current Opinion in Pharmacology*, *3*, 73–77. doi:10.1016/S1471-4892(02)00016-4

- Patel, K., Guralnik, J., Dansie, E., & Turk, D. (2013). Prevalence and Impact of Pain among Older Adults in the United States: Findings from the 2011 National Health and Aging Trends Study. *Pain, 154*(12), 1–13. doi:10.1016/j.biotechadv.2011.08.021.Secured
- Payne, B., & Norfleet, M. (1986). Chronic pain and the family: A review. *Pain, 26*(1), 1–22. doi:10.1016/0304
- Payne, K., Varon, S. F., Kawata, a. K., Yeomans, K., Wilcox, T. K., Manack, A., ... Blumenfeld, M. (2011). The International Burden of Migraine Study (IBMS): Study design, methodology, and baseline cohort characteristics. *Cephalalgia, 31*(10), 1116–1130. <http://doi.org/10.1177/0333102411410610>
- Pearce, J. M. S. (1986). Historical aspects of migraine. *Journal of Neurology, Neurosurgery, and Psychiatry, 1097–1103*.
- Pearce, J. M. S. (2013). The Neurology of Aretaeus: Radix Pedis Neurologia. *European Neurology, 70*, 106–112. doi:10.1159/000352031
- Pengpid, S., Peltzer, K., & Van der Heever, H. (2011). Prevalence of alcohol use and associated factors in urban hospital outpatients in South Africa. *International Journal of Environmental Research and Public Health, 8*(7), 2629–39. doi:10.3390/ijerph8072629
- Perlis, N., Krahn, M., Alibhai, S., Finelli, A., Ritvo, P., Bremner, K. E., & Kulkarni, G. (2014). Conceptualizing global health-related quality of life in bladder cancer. *Quality of Life Research, 23*(8), 2153–2167. doi:10.1007/s11136-014-0685-9
- Pestana, E., Belak, S., Diallo, A., Crowther, J., & Viljoen, G. (2010a). *Early, rapid and sensitive veterinary molecular diagnostics-real time PCR applications*. Dordrecht: Springer. Retrieved from <http://www.lavoisier.fr/livre/notice.asp?ouvrage=2429509>

- Peters, M., Abu-Saad, H. H., Robbins, I., Vydelingum, V., Dowson, A., & Murphy, M. (2005). Patients' management of migraine and chronic daily headache: a study of the members of the Migraine Action Association (United Kingdom). *Headache*, *45*(5), 571–81. doi:10.1111/j.1526-4610.2005.05111.x
- Petroff, O. a C., Errante, L. D., Rothman, D. L., Kim, J. H., & Spencer, D. D. (2002). Glutamate-glutamine cycling in the epileptic human hippocampus. *Epilepsia*, *43*(7), 703–710. doi:10.1046/j.1528-1157.2002.38901.x
- Phoenix, C., Osborne, N. J., Redshaw, C., Moran, R., Stahl-Timmins, W., Depledge, M. H., ... Wheeler, B. W. (2013). Paradigmatic approaches to studying environment and human health: (Forgotten) implications for interdisciplinary research. *Environmental Science & Policy*, *25*, 218–228. doi:10.1016/j.envsci.2012.10.015
- Pietrobon, D. (2005). Migraine: new molecular mechanisms. *The Neuroscientist*, *11*(4), 373–86. doi:10.1177/1073858405275554
- Pompili, M., Di Cosimo, D., Innamorati, M., Lester, D., Tatarelli, R., & Martelletti, P. (2009). Psychiatric comorbidity in patients with chronic daily headache and migraine : a selective overview including personality traits and suicide risk. *Journal of Headache Pain*, *10*, 283–290. doi:10.1007/s10194-009-0134-2
- Pompili, M., Serafini, G., Di Cosimo, D., Dominici, G., Innamorati, M., Lester, D., ... Martelletti, P. (2010). Psychiatric comorbidity and suicide risk in patients with chronic migraine. *Neuropsychiatric Disease and Treatment*, *6*, 81–91. Retrieved from <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2854084&tool=pmcentrez&rendertype=abstract>

- Porter-Moffitt, S., Gatchel, R. J., Robinson, R. C., Deschner, M., Posamentier, M., Polatin, P., & Lou, L. (2006). Biopsychosocial profiles of different pain diagnostic groups. *The Journal of Pain : Official Journal of the American Pain Society*, 7(5), 308–18.
doi:10.1016/j.jpain.2005.12.003
- Practical Haemostasis.com. (2016). Activated Partial Thromboplastin Time (APTT). Retrieved May 19, 2016, from [http://www.practical-haemostasis.com/Screening Tests/aptt.html](http://www.practical-haemostasis.com/Screening%20Tests/aptt.html)
- Pragodpol, P., & Ryan, C. (2013). Critical review of factors predicting health-related quality of life in newly diagnosed coronary artery disease patients. *Journal of Cardiovascular Nursing*, 28(3), 277–284.
- Preanalytix. (2015). *PAXgene Blood RNA Kit Handbook*. Retrieved from http://www.preanalytix.com/sites/default/files/handbooks/HB-0181-003_1051084_151017219_V2_R2_HB_PAX_Blood_RNA_0615_US_CA.pdf
- Prehn, K., Wartenburger, I., Mériaux, K., Scheibe, C., Goodenough, O. R., Villringer, A., ... Heekeren, H. R. (2007). Individual differences in moral judgment competence influence neural correlates of socio-normative judgments. *Social Cognitive and Affective Neuroscience*, 3(1), 33–46. doi:10.1093/scan/nsm037
- Qiagen. (2011a). *QuantiTect SYBR Green PCR Handbook*. Retrieved from <file:///C:/Users/govenco/Downloads/EN-QuantiTect-SYBR-Green-PCR-Handbook.pdf>
- Qiagen. (2011b). *RT2 Profiler Pathway “ Signature ” PCR Array Handbook*. California: Qiagen. Retrieved from <http://pcrdataanalysis.sabiosciences.com/wnt/RT2ProfilerSignaturePCRArrayHandbook.pdf>
- Qiagen. (2012). RT² Profiler™ PCR Array System Controls. Retrieved March 18, 2016, from <http://www.sabiosciences.com/pcrarraycontrols.php>

- Qiagen. (2015). RT qPCR Primer Assay Handbook. Retrieved from
file:///C:/Users/govenco/Downloads/EN-RT2-qPCR-Primer-Assay-Handbook_0815
(1).pdf
- Racine, M., Tousignant-laflamme, Y., Kloda, L. A., Dion, D., Dupuis, G., & Choinière, M.
(2012). A systematic literature review of 10 years of research on sex / gender and pain
perception – Part 2 : Do biopsychosocial factors alter pain sensitivity differently in
women and men ?, *153*, 619–635. doi:10.1016/j.pain.2011.11.026
- Radat, F., Creac'h, C., Guegan-Massardier, E., Mick, G., Guy, N., Fabre, N., ... Lantéri-Minet,
M. (2008). Behavioral dependence in patients with medication overuse headache: a cross-
sectional study in consulting patients using the DSM-IV criteria. *Headache*, *48*(7), 1026–
36. doi:10.1111/j.1526-4610.2007.00999.x
- Radat, F., Mekies, C., Géraud, G., Valade, D., Vivès, E., Lucas, C., Lantéri-Minet, M. (2008).
Anxiety, stress and coping behaviours in primary care migraine patients: results of the
SMILE study. *Cephalalgia : An International Journal of Headache*, *28*(11), 1115–25.
doi:10.1111/j.1468-2982.2008.01644.x
- Raggi, A., Giovannetti, A. M., Quintas, R., D'Amico, D., Cieza, A., Sabariego, C., Leonardi, M.
(2012). A systematic review of the psychosocial difficulties relevant to patients with
migraine. *The Journal of Headache and Pain*, *13*(8), 595–606. doi:10.1007/s10194-012-
0482-1
- Rainero, I., Dall'Omo, A. M., Rubino, E., Valfrè, W., Fasano, M. E., Rivoiro, C., Pinessi, L.
(2006). HLA-DRB1 genotyping in Italian migraine patients. *Neuroscience Letters*, *393*(2-
3), 90–3. doi:10.1016/j.neulet.2005.08.071

- Rainesalo, S., Keränen, T., Saransaari, P., & Honkaniemi, J. (2005). GABA and glutamate transporters are expressed in human platelets. *Molecular Brain Research*, *141*(2), 161–5. doi:10.1016/j.molbrainres.2005.08.013
- Raistrick, D., Bradshaw, J., Tober, G., Weiner, J., Allison, J., & Healey, C. (1994). Development of the Leeds Dependence Questionnaire (LDQ): A questionnaire to measure alcohol and opiate dependence in the context of a treatment evaluation package. *Addiction*, *89*(5), 563–572. doi:10.1111/j.1360-0443.1994.tb03332.x
- Ramadan, N. (2003). The link between glutamate and migraine. *CNS Spectrums*, *8*(6), 446–449.
- Randhawa, G. (1998). An exploratory study examining the influence of religion on attitudes towards organ donation among the Asian population in Luton, UK. *Nephrology Dialysis Transplantation*, *13*(8), 1949–1954. <http://doi.org/10.1093/ndt/13.8.1949>
- Rasmussen, B. K. (1995). Headache and migraine Epidemiology of migraine. *Biomedicine & Pharmacotherapy*, *49*(I), 452–455.
- Rasmussen, B., Jensen, R., Schroll, M., & Olesen, J. (1995). Epidemiology of migraine. *Journal of Clinical Epidemiology*, *44*(11), 1147–1157.
- Richman, H., & Frueh, B. C. (1997). Personality and PTSD II: personality assessment of PTSD-diagnosed Vietnam veterans using the cloning tridimensional personality questionnaire (TPQ). *Depression and Anxiety*, *6*(2), 70–7. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9451548>
- Ritsner, M., Gibel, A., & Ratner, Y. (2006). Determinants of changes in perceived quality of life in the course of schizophrenia. *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *15*(3), 515–26. doi:10.1007/s11136-005-2808-9

- Robbins, M. S., Lipton, R. B., Laureta, E. C., & Grosberg, B. M. (2009). CACNA1A nonsense mutation is associated with basilar-type migraine and episodic ataxia type 2. *Headache*, 49(7), 1042–6. doi:10.1111/j.1526-4610.2009.01464.x
- Rodero, B., Casanueva, B., Luciano, J. V, Gili, M., Serrano-Blanco, A., & García-Campayo, J. (2011). Relationship between behavioural coping strategies and acceptance in patients with fibromyalgia syndrome: elucidating targets of interventions. *BMC Musculoskeletal Disorders*, 12, 143. doi:10.1186/1471-2474-12-143
- Rosenstock, H. A., & Cambor, C. G. (1979). Family therapy approach to incapacitating migraine. *International Journal of Family Therapy*, 1(1), 46–55. doi:10.1007/BF00926788
- Roskies, A. (2002). Neuroethics for the new millenium. *Neuron*, 35, 21–23. doi:10.1016/S0896-6273(02)00763-8
- Ross, S. D., Fahrbach, K., Frame, D., Scheye, R., Connelly, J. E., & Glaspy, J. (2003). The effect of anemia treatment on selected health-related quality-of-life domains: a systematic review. *Clinical Therapeutics*, 25(6), 1786–805. doi:10.1016/S0149-2918(03)80170-4
- Rothrock, J. F. (2010). The riddle of migraine's biogenesis. *Headache*, 50(6), 963–964. doi:10.1111/j.1526-4610.2010.01686.x
- Rubino, E., Fenoglio, P., Gallone, S., Govone, F., Vacca, A., Martino, P. De, Rainero, I. (2013). Genetic variants in the NOTCH4 gene influence in the clinical features of migraine, 14(1), 1. doi:10.1186/1129-2377-14-28
- Rueda, M. R., & Rothbart, M. K. (2009). The Influence of Temperament on the Development of Coping: The Role of Maturation and Experience, (124), 19–31. doi:10.1002/cd

- Rueda, M., & Rothbart, M. (2009). The influence of temperament on the development of coping: The role of maturation and experience. In E. Skinner & M. Zimmer-Gembeck (Eds.), *Coping and the development of regulation* (pp. 19–31). San Francisco: Jossey-Bass.
doi:10.1002/cd
- Russell, M. B., Rasmussen, B. K., Fenger, K., & Olesen, J. (1996). Migraine without aura and migraine with aura are distinct clinical entities: A study of four hundred and eighty-four male and female migraineurs from the general population. *Cephalalgia*, *16*(4), 239–245.
doi:10.1046/j.1468-2982.1996.1604239.x
- Russell, M. B., Ulrich, V., Gervil, M., & Olesen, J. (2002). Migraine without aura and migraine with aura are distinct disorders. A population-based twin survey. *Headache*, *42*(5), 332–6.
- Ryan, A. B. (2006). Post-positivist approaches to research. Retrieved from
http://eprints.maynoothuniversity.ie/874/1/post-positivist_approaches_to_research.pdf
- Sabo, T., & Maddox, M. (2009). *Headache Questionnaire*. Aurora: The Headache Clinic at The Children's Hospital.
- Sacco, S., Ricci, S., Degan, D., & Carolei, A. (2012). Migraine in women: the role of hormones and their impact on vascular diseases. *Journal of Headache Pain*, *13*(3), 177–189.
- Sales, P., Carvalho, A., McIntyre, R., Pavlidis, N., & Hypantis, T. (2014). Psychosocial predictors of health outcomes in colorectal cancer: A comprehensive review. *Cancer Treatment Reviews*, *40*(6), 800–809.
- Sánchez-Román, S., Téllez-Zenteno, J. F., Zermeño-Phols, F., García-Ramos, G., Velázquez, A., Derry, P., Guevara-López, U. M. (2007). Personality in patients with migraine evaluated

- with the “Temperament and Character Inventory”. *The Journal of Headache and Pain*, 8(2), 94–104. doi:10.1007/s10194-007-0352-9
- Santanello, N. C., Davies, G., Allen, C., Kramer, M., & Lipton, R. (2002). Determinants of migraine-specific quality of life. *Cephalalgia*, 22(16), 680–685. doi:10.1046/j.1468-2982.2002.00435.x
- Sarason, I., Sarason, B., Shearin, E., & Pierce, G. (1987). A brief measure of social support: Practical and theoretical implications. *Journal of Social and Personal Relationships*, 4, 497–510.
- Sarchielli, P., Di Filippo, M., Nardi, K., & Calabresi, P. (2007). Sensitization, glutamate, and the link between migraine and fibromyalgia. *Current Pain and Headache Reports*, 11(5), 343–51.
- Sauro, K. M., & Becker, W. J. (2009). The Stress and Migraine Interaction. *Headache*, 49(9), 1378–1386.
- Schalock, R. L. (1994). The concept of quality of life and its current application in the field of mental retardation / developmental disabilities. In D. Goode (Ed.), *Quality of life for persons with disabilities: International perspectives and issues*. (pp. 266–284). Cambridge: Brookline Books.
- Schalock, R. L. (1994). The concept of quality of life and its current application in the field of mental retardation / developmental disabilities. In D. Goode (Ed.), *Quality of life for persons with disabilities: International perspectives and issues*. (pp. 266–284). Cambridge: Brookline Books.
- Schalock, R. L., Brown, I., Brown, R., Cummins, R., Felce, D., Matikka, L., Parmenter, T. (2002). Conceptualization, measurement, and application of quality of life for persons

- with intellectual disabilities: report of an international panel of experts. *Mental Retardation*, 40(6), 457–470. doi:10.1352/0047-6765(2002)040<0457:CMAAOQ>2.0.CO;2
- Schleifer, S., Marbach, J., & Keller, S. (1990). Psychoneuroimmunology: Potential Relevance to Chronic Orofacial Pain. *Anesthesia Progress*, 34, 93–98. Retrieved from <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2190324/>
- Schoenen, J. (2006). Neurophysiological features of the migrainous brain. *Neurological Sciences*, 27(SUPPL. 2). doi:10.1007/s10072-006-0575-1
- Schürks, M. (2012). Genetics of migraine in the age of genome-wide association studies. *The Journal of Headache and Pain*, 13(1), 1–9. <http://doi.org/10.1007/s10194-011-0399-0>
- Schürks, M., Buring, J. E., & Kurth, T. (2009). Agreement of self-reported migraine with ICHD-II criteria in the Women's Health Study. *Cephalalgia*, 29(10), 1086–1090. doi:10.1111/j.1468-2982.2008.01835.x
- Schurks, M., Rist, P. M., Bigal, M. E., Buring, J. E., Lipton, R. B., & Kurth, T. (2009). Migraine and cardiovascular disease: systematic review and meta-analysis. *British Medical Journal*, 339, b3914–b3914. doi:10.1136/bmj.b3914
- Schwartz, G. E. (1982). Testing the biopsychosocial model: The ultimate challenge facing behavioral medicine? *Journal of Consulting and Clinical Psychology*, 50(6), 1040–1053. doi:10.1037//0022-006X.50.6.1040
- Schwedt, T., & Dodick, D. (2009). Advanced neuroimaging of migraine. *Lancet Neurology*, 8(6), 560–568.
- Schwenzer, K. (2008). Protecting vulnerable subjects in clinical research: children, pregnant women, prisoners, and employees. *Respiratory Care*, 53(10), 1342–9. Retrieved from

<http://rc.rcjournal.com/content/53/10/1342.short>

SeraCare Life Sciences. (2013). *ELISA Technical Guide*. Gaithersburg: KPL.

Sharma, K., Singh, S., & Remanan, R. (2013). Quality of life and psychiatric co-morbidity in Indian migraine patients: A headache clinic sample. *Neurology India*, *61*(4), 355.
doi:10.4103/0028-3886.117584

Sharp, E. (2016). Interdisciplinary experiences : a postgraduate geographer's perspective, *8265*(February). <http://doi.org/10.1080/03098265.2014.956295>

Shavers-Hornaday, V. L., Lynch, C. F., Burmeister, L. F., & Torner, J. C. (1997). Why are African Americans under-represented in medical research studies? Impediments to participation. *Ethnicity & Health*, *2*(1–2), 31–45.
<http://doi.org/10.1080/13557858.1997.9961813>

Sher, K. J., Wood, M. D., Crews, T. M., & Vandiver, P. a. (1995). The Tridimensional Personality Questionnaire: Reliability and validity studies and derivation of a short form. *Psychological Assessment*, *7*(2), 195–208. doi:10.1037//1040-3590.7.2.195

Shevel, E. (2011). The extracranial vascular theory of migraine--a great story confirmed by the facts. *Headache*, *51*(3), 409–17. doi:10.1111/j.1526-4610.2011.01844.x

Shevel, E., & Shevel, D. (2014). The international headache society classification of migraine headache - A call for substantiating data. *Journal of Biomedical Science and Engineering*, *7*, 112–114.

Shin, H.-E., Han, S.-J., Lee, K.-S., & Park, J.-W. (2011). Polymorphism of the Glutamate Transporter Protein EAAT2 and Migraine Transformation into Chronic Daily Headache. *Journal of Clinical Neurology (Seoul, Korea)*, *7*(3), 143–7. doi:10.3988/jcn.2011.7.3.143

- Shiroiwa, T., Fukuda, T., Ikeda, S., Igarashi, A., Noto, S., Saito, S., & Shimozuma, K. (2015). Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. *Quality of Life Research*, 1–13. doi:10.1007/s11136-015-1108-2
- Shneker, B. F., & Fountain, N. B. (2003). Epilepsy. *Disease-a-Month*, 49(7), 426–478.
[http://doi.org/10.1016/S0011-5029\(03\)00065-8](http://doi.org/10.1016/S0011-5029(03)00065-8)
- Sieberg, C. B., Huguet, A., von Baeyer, C. L., & Seshia, S. (2012). Psychological interventions for headache in children and adolescents. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, 39(1), 26–34. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/22384492>
- Sikandar, S., Ronga, I., Iannetti, G. D., & Dickenson, A. H. (2013). Neural coding of nociceptive stimuli - From rat spinal neurones to human perception. *Pain*, 154(8), 1263–1273.
doi:10.1016/j.pain.2013.03.041
- Silberstein, S. D., Neto, W., Schmitt, J., & Jacobs, D. (2004). Topiramate in migraine prevention: results of a large controlled trial. *Archives of Neurology*, 61(4), 490–5.
doi:10.1001/archneur.61.4.490
- Silberstein, S. D., Olesen, J., Bousser, M., Diener, H., Dodick, D., First, M., Lainez, M. J. A. (2005). The International Classification of Headache Disorders , 2nd Edition (ICHD-II)- revision of criteria for 8 . 2 Medication-overuse headache. *Cephalalgia*, 25, 460–465.
- Singh, A. K., Shukla, R., Trivedi, J. K., & Singh, D. (2013). Association of psychiatric co-morbidity and efficacy of treatment in chronic daily headache in Indian population. *Journal of Neurosciences in Rural Practice*, 4(2), 132–139. doi:10.4103/0976-3147.112736

- Skipstein, A., Janson, H., & Kjeldsen, A. (2012). Trajectories of maternal symptoms of depression and anxiety over 13 years: the influence of stress, social support, and maternal temperament. *BMC Public Health, 12*(1120). Retrieved from <http://www.biomedcentral.com/1471-2458/12/1120/>
- Skomo, M. L., Desselle, S. P., & Berdine, H. J. (2006). Factors influencing migraineur-consulting behavior in a university population. *Headache, 46*(5), 742–9. doi:10.1111/j.1526-4610.2006.00431.x
- Slavich, G. M., & Cole, S. W. (2013). The Emerging Field of Human Social Genomics. *Clinical Psychological Science, 1*(3), 331–348. doi:10.1177/2167702613478594
- Smith, G. C., & Strain, J. J. (2002). George Engel's contribution to clinical psychiatry. *Australian and New Zealand Journal of Psychiatry, 36*(4), 458–466. doi:10.1046/j.1440-1614.2002.t01-1-01036.x
- Smith, R. (1998). Impact of migraine on the family. *Headache, 38*(6), 423–6. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/9664745>
- Soh, S., Morris, M., & McGinley, J. (2011). Determinants of health-related quality of life in Parkinson's disease: A systematic review. *Parkinsonism Related Disorders, 17*(1), 1–9.
- Solms, M., & Turnbull, O. (2002). *The brain and the inner world: An introduction to the neuroscience of subjective experience*. London: H. Karnac.
- Sousa, K. H., & Kwok, O.-M. (2006). Putting Wilson and Cleary to the test: analysis of a HRQOL conceptual model using structural equation modeling. *Quality of Life Research : An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation, 15*(4), 725–737. doi:10.1007/s11136-005-3975-4

- Sovio, U., King, V., Miettunen, J., Ek, E., Laitinen, J., Joukamaa, M., Järvelin, M.-R. (2007). Cloninger's Temperament dimensions, socio-economic and lifestyle factors and metabolic syndrome markers at age 31 years in the Northern Finland Birth Cohort 1966. *Journal of Health Psychology, 12*(2), 371–82. doi:10.1177/1359105307074301
- Spiegel, B. M. R., Melmed, G., Robbins, S., & Esrailian, E. (2008). Biomarkers and Health-Related Quality of Life in End-Stage Renal Disease: A Systematic Review. *Clinical Journal of the American Society of Nephrology, 3*(6), 1759–1768.
doi:10.2215/CJN.00820208
- Spiegelaere, W. De, Dern-wieloch, J., Weigel, R., Schumacher, V., Vandekerckhove, L., & Fink, C. (2015). Reference Gene Validation for RT-qPCR , a Note on Different Available Software Packages. *PLOSOne, March*, 1–13. doi:10.1371/journal.pone.0122515
- Spierings, E. (2001). Migraine, Big and Small. *Headache, 41*, 918–920. Retrieved from http://adsabs.harvard.edu/cgi-bin/nph-data_query?bibcode=2010arXiv1004.4279E&link_type=ABSTRACT
- Statistics South Africa. (2014). *Mid-year Population estimates*. doi:Statistical release P0302
- Stebbins, R. (Ed.). (2001). *Exploratory research in the social sciences*. Thousand Oaks: SAGE Publications.
- Stephens, R. (1998). Quality of life in cancer patients. *Hospital Medicine, 59*(9), 737.
doi:10.1097/00124363-200004000-00002
- Steiner, T. J., Stovner, L. J., & Birbeck, G. L. (2013). Migraine: The seventh disabling. *Headache*. <http://doi.org/10.1111/head.12034>
- Stel, H. F. van, & Buskens, E. (2006). Comparison of the SF-6D and the EQ-5D in patients with coronary heart disease. *Health and Quality of Life Outcomes, 4*(1), 20.

<http://doi.org/10.1186/1477-7525-4-20>

Stephens, R. (1998). Quality of life in cancer patients. *Hospital Medicine*, 59(9), 737.

<http://doi.org/10.1097/00124363-200004000-00002>

Stewart, M. E., Ebmeier, K. P., & Deary, I. J. (2004). The structure of Cloninger's

Tridimensional Personality Questionnaire in a British sample. *Personality and Individual Differences*, 36(6), 1403–1418. doi:10.1016/S0191-8869(03)00237-X

Stewart, W., Simon, D., Shechter, A., & Lipton, R. (1995). Population variation in migraine prevalence: A meta-analysis. *Journal of Clinical Epidemiology*, 48(2), 269–280.

Stokes, M., Becker, W. J., Lipton, R. B., Sullivan, S. D., Wilcox, T. K., Wells, L., ... Stokes, C.

M. (2011). Cost of Health Care Among Patients With Chronic and Episodic Migraine in Canada and the USA : Results From the International Burden of Migraine Study (IBMS), 1058–1077. <http://doi.org/10.1111/j.1526-4610.2011.01945.x>

Stovner, L., Hagen, K., Jensen, R., Katsarava, Z., Lipton, R., Scher, A., Zwart, J. (2007). The

global burden of headache: a documentation of headache prevalence and disability worldwide. *Cephalalgia : An International Journal of Headache*, 27(3), 193–210.

doi:10.1111/j.1468-2982.2007.01288.x

Striessnig, J. (2005). Pathophysiology of migraine headache: Insight from pharmacology and

genetics. *Drug Discovery Today: Disease Mechanisms*, 2(4), 453–462.

doi:10.1016/j.ddmec.2005.11.002

Stronks, D. L., Tulen, J. H., Peppinkhuizen, L., Verheij, R., Mantel, G. W., Spinhoven, P., &

Passchier, J. (1999). Personality traits and psychological reactions to mental stress of female migraine patients. *Cephalalgia : An International Journal of Headache*, 19(6),

566–74. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10448543>

- Stroud, M. W., Thorn, B. E., Jensen, M. P., & Boothby, J. L. (2000). The relation between pain beliefs, negative thoughts, and psychosocial functioning in chronic pain patients. *Pain, 84*(2-3), 347–52. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10666540>
- Sullivan, M. J. L. (2009). *The Pain Catastrophizing Scale user manual*. Montreal: McGill University.
- Sullivan, M. J. L., Rouse, D., & Bishop, S. (1997). Thought Suppression, Catastrophizing, and Pain. *Cognitive Therapy and Research, 21*(5), 555–568.
- Sullivan, M. J. L., Thorn, B., Haythornthwaite, J. A., Keefe, F., Martin, M., Bradley, L. A., & Lefebvre, J. C. (2001). Theoretical Perspectives on the Relation Between Catastrophizing and Pain. *The Clinical Journal of Pain, 17*, 52–64.
- Suls, J., & Rothman, A. (2004). Evolution of the biopsychosocial model: prospects and challenges for health psychology. *Health Psychology, 23*(2), 119–25. doi:10.1037/0278-6133.23.2.119
- Suvinen, T. I., Reade, P. C., Kemppainen, P., Könönen, M., & Dworkin, S. F. (2005). Review of aetiological concepts of temporomandibular pain disorders: towards a biopsychosocial model for integration of physical disorder factors with psychological and psychosocial illness impact factors. *European Journal of Pain, 9*(6), 613–33. doi:10.1016/j.ejpain.2005.01.012
- Swenson, J. R., & Clinch, J. J. (2000). Assessment of quality of life in patients with cardiac disease: the role of psychosomatic medicine. *Journal of Psychosomatic Research, 48*, 405–415.

- Taillefer, M., Dupuis, G., Roberge, M., & Le May, S. (2003). Health-related quality of life models: Systematic review of the literature. *Social Indicators Research*, *64*(2), 293–323. doi:10.1023/A:1024740307643
- Tajvar, M., Arab, M., & Montazeri, A. (2008). Determinants of health-related quality of life in elderly in Tehran, Iran. *BMC Public Health*, *8*(1), 323. doi:10.1186/1471-2458-8-323
- Takano, T., & Nedergaard, M. (2009). Deciphering migraine. *The Journal of Clinical Investigation*, *119*(1), 16–19. doi:10.1172/JCI38051.16
- Tarlov, C., Ware, J. J., Greenfield, S., Nelson, E., Perrin, E., & Zubkoff, M. (1989). The Medical Outcomes Study. An application of methods for monitoring the results of medical care. *Journal of the American Medical Association*.
- Taylor, R., Sander, J., Taylor, R., & Baker, G. (2011). Predictors of health-related quality of life and costs in adults with epilepsy: A systematic review. *Epilepsia*, *52*(12), 168–180.
- Theeler, B. J., & Erickson, J. C. (2009). Mild head trauma and chronic headaches in returning US soldiers. *Headache*, *49*(4), 529–534. <http://doi.org/10.1111/j.1526-4610.2009.01345.x>
- Theoharides, T. C., Donelan, J., Kandere-grzybowska, K., & Konstantinidou, A. (2005). The role of mast cells in migraine pathophysiology. *Brain Research Reviews*, *49*, 65–76. doi:10.1016/j.brainresrev.2004.11.006
- Thorn, B. E., Pence, L. B., Ward, L. C., Kilgo, G., Clements, K. L., Cross, T. H., Tsui, P. W. (2007). A randomized clinical trial of targeted cognitive behavioral treatment to reduce catastrophizing in chronic headache sufferers. *The Journal of Pain : Official Journal of the American Pain Society*, *8*(12), 938–49. doi:10.1016/j.jpain.2007.06.010

- Tichopad, A., Kitchen, R., Riedmaier, I., Becker, C., & Ståhlberg, A. (2009). Design and Optimization of Reverse-Transcription Quantitative PCR Experiments
CONCLUSIONS :, 000, 1–8. doi:10.1373/clinchem.2009.126201
- Tietjen, G. E., & Peterlin, B. L. (2011). Childhood Abuse and Migraine: Epidemiology, Sex Differences, and Potential Mechanisms. *Headache: The Journal of Head and Face Pain*, 51(6), 869–879. doi:10.1111/j.1526-4610.2011.01906.x
- Tietjen, G. E., Brandes, J. L., Peterlin, B. L., Eloff, A., Dafer, R. M., Stein, M. R., Khuder, S. a. (2010a). Childhood maltreatment and migraine (part II). Emotional abuse as a risk factor for headache chronification. *Headache*, 50(1), 32–41. doi:10.1111/j.1526-4610.2009.01557.x
- Tietjen, G. E., Brandes, J. L., Peterlin, B. L., Eloff, A., Dafer, R. M., Stein, M. R., Khuder, S. a. (2010b). Childhood maltreatment and migraine (part III). Association with comorbid pain conditions. *Headache*, 50(1), 42–51. doi:10.1111/j.1526-4610.2009.01558.x
- Tietjen, G. E., Brandes, J. L., Peterlin, B. L., Eloff, A., Dafer, R. M., Stein, M. R., Khuder, S. a. (2010c). Childhood Maltreatment and Migraine (Part I). Prevalence and Adult Revictimization: A Multicenter Headache Clinic Survey. *Headache: The Journal of Head and Face Pain*, 50(1), 20–31. doi:10.1111/j.1526-4610.2009.01556.x
- Tietjen, G. E., & Peterlin, B. L. (2011). Childhood Abuse and Migraine: Epidemiology, Sex Differences, and Potential Mechanisms. *Headache: The Journal of Head and Face Pain*, 51(6), 869–879. <http://doi.org/10.1111/j.1526-4610.2011.01906.x>
- Torrance, G., & Feeny, D. (1989). Utilities and Quality-Adjusted Life Years. *International Journal of Technology Assessment in Health*, 5(4), 559–575.
- Truchon, M., & Fillion, L. (2000). Biopsychosocial Determinants of Chronic Disability and Low

- Back Pain : A Review . *Journal of Occupational Rehabilitation*, 10(2), 117–142.
- Tsigos, C., & Chrousos, G. P. (2002). Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. *Journal of Psychosomatic Research*, 53(4), 865–871.
doi:10.1016/S0022-3999(02)00429-4
- Tuner, D.P., & Houle, T.T. Psychological evaluation of the primary headache patient. (2013).
Pain Management, 3(1), 19-25.
- Unger, J. (2006). Migraine headaches: a historical prospective, a glimpse into the future, and migraine epidemiology. *Disease-a-Month : DM*, 52(10), 367–84.
doi:10.1016/j.disamonth.2006.09.002
- University College London Hospitals. (2012). Unfractionated Heparin (UFH) for systemic anticoagulation - ADULTS. Retrieved May 19, 2016, from
http://www.uclhguide.com/fragr_image/media/heparin
- University of Minnesota Medical Center, Fairview Collaborative Studies Clinical Laboratory
Minneapolis, M. (n.d.). *Laboratory Procedure Manual: Fasting glucose in plasma*.
Minneapolis: University of Minnesota Medical Center.
- University of Sheffield. (n.d.). Measuring and valuing health. Retrieved from
<https://www.futurelearn.com/courses/valuing-health>
- University of South Africa. (2006). *Unisa Research policy*. Pretoria.
- Vaccaro, M., Riva, C., Tremolizzo, L., Longoni, M., Aliprandi, A., Agostoni, E., Ferrarese, C. (2007). Platelet glutamate uptake and release in migraine with and without aura.
Cephalalgia : An International Journal of Headache, 27(1), 35–40. doi:10.1111/j.1468-2982.2006.01234.x

- Vallejo-Illarramendi, A., Domercq, M., Pérez-Cerdá, F., Ravid, R., & Matute, C. (2006). Increased expression and function of glutamate transporters in multiple sclerosis. *Neurobiology of Disease*, *21*(1), 154–64. doi:10.1016/j.nbd.2005.06.017
- Van Eeghem, H. (2005). Gedragstherapeutische mogelijkheden bij migraine. *Gedragstherapie*, *38*(3), 175–192. Retrieved from <http://psycnet.apa.org/psycinfo/2005-12106-001>
- Vargas, B. B. (2009). Chronic migraine: current pathophysiologic concepts as targets for treatment. *Current Pain and Headache Reports*, *13*(1), 64–6. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/19126374>
- Verrotti, A., Coppola, G., Fonzo, A. Di, & Tozzi, E. (2011). Should “migralepsy” be considered an obsolete concept? A multicenter retrospective clinical/EEG study and review of the literature. *Epilepsy & Behavior*, *21*(1), 52–9. <http://doi.org/10.1016/j.yebeh.2011.03.004>
- Verweij, K. J. H., Zietsch, B. P., Medland, S. E., Gordon, S. D., Benyamin, B., Nyholt, D. R., Wray, N. R. (2010). A genome-wide association study of Cloninger’s temperament scales: implications for the evolutionary genetics of personality. *Biological Psychology*, *85*(2), 306–17. doi:10.1016/j.biopsycho.2010.07.018
- Vikelis, M. (2007). The role of glutamate and its receptors in migraine. *CNS Neurological Disorder Drug Targets*, *6*(4), 251–258.
- Vilhena, E., Pais-Ribeiro, J., Silva, I., Pedro, L., Meneses, R. F., Cardoso, H., Mendonça, D. (2014). Psychosocial factors as predictors of quality of life in chronic portuguese patients. *Health and Quality of Life Outcomes*, *12*(1), 3. doi:10.1186/1477-7525-12-3
- Villalón, C. M., & Olesen, J. (2009). Pharmacology & Therapeutics The role of CGRP in the pathophysiology of migraine and efficacy of CGRP receptor antagonists as acute

- antimigraine drugs. *Pharmacology and Therapeutics*, 124(3), 309–323.
doi:10.1016/j.pharmthera.2009.09.003
- Viola, S., Viola, P., Litterio, P., Buongarzone, M. P., & Fiorelli, L. (2012). Stroke risk and migraine: near-infrared spectroscopy study. *Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, 33 Suppl 1(November 2011), S173-5. <http://doi.org/10.1007/s10072-012-1077-y>
- Vos, J., & Passchier, J. (2003). Reduced impact of migraine in everyday life: an observational study in the Dutch Society of Headache Patients. *Headache*, 43(6), 645–50. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12786925>
- Vowles, K.E., & McCracken, L.M. (2008). Acceptance and values-based action in chronic pain: a study of treatment effectiveness and process. *Journal of Consulting and Clinical Psychology*, 76(3), 397-407.
- Vranceanu, A., Hageman, M., Strooker, J., Vrahas, M., & Ring, D. (2015). A preliminary RCT of a mind body skills based intervention addressing mood and coping strategies in patients with acute orthopaedic trauma. *Injury*, 46(4), 552–557.
<http://doi.org/10.1016/j.injury.2014.11.001>
- Wang, S. (2003). Epidemiology of migraine and other types of headache in Asia. *Current Neurology and Neuroscience Reports*, 3(2), 104–8. Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/12583837>
- Wang, S., Fuh, J., Lu, S., & Juang, K. (2001). Quality of life differs among headache diagnoses: Analysis of SF-36 survey in 901 headache patients. *Pain*, 89(2-3), 285–292.
- Wang, S.-J., Chen, P.-K., & Fuh, J.-L. (2010). Comorbidities of migraine. *Frontiers in Neurology*, 1(August), 16. <http://doi.org/10.3389/fneur.2010.00016>

- Ware, J. E. (2004). Pre-Publication Version: SF-36 Health Survey Update, 1–51. Retrieved from papers2://publication/uuid/7743391D-32B5-4F03-A884-F517B5D972AE
- Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-Short-Form Health Survey (SF-36). *Medical Care*, 30(6), 473–483.
- Weatherall, M. W. (2012). The migraine theories of Liveing and Latham: a reappraisal. *Brain : A Journal of Neurology*, 135(Pt 8), 2560–8. doi:10.1093/brain/aws020
- Wellman, R. (n.d.). The supremacy of method: An outline of Dewey's theory of inquiry. Retrieved from <http://people.umass.edu/~rwellman/Philosophy/DeweyMethod.pdf>
- Wendt, J., Cady, R., Singer, R., & Peters, K. (2006). A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine. *Clinical Therapeutics*, 328(4), 517–526. Retrieved from <http://europepmc.org/abstract/MED/16750463>
- Wendt, J., Cady, R., Singer, R., Peters, K., Webster, C., Kori, S.,... View, M. (2006). A Randomized , Double-Blind , Placebo-Controlled Trial of the Efficacy and Tolerability of a 4-mg Dose of Subcutaneous Sumatriptan for the Treatment of Acute Migraine Attacks in Adults. *Clinical Therapeutics*, 28(4), 517–526.
- Whillier, S., Garcia, B., Chapman, B. E., Kuchel, P. W., & Raftos, J. E. (2011). Glutamine and α -ketoglutarate as glutamate sources for glutathione synthesis in human erythrocytes. *FEBS Journal*, 278(17), 3152–3163. doi:10.1111/j.1742-4658.2011.08241.x
- Wieser, T., Walliser, U., Womastek, I., & Kress, H. G. (2012). Dysfunctional coping in headache: avoidance and endurance is not associated with chronic forms of headache. *European Journal of Pain (London, England)*, 16(2), 268–77. doi:10.1016/j.ejpain.2011.06.011

- Wills, T., Sandy, J., & Yaeger, A. (2000). Temperament and adolescent substance use: an epigenetic approach to risk and protection. *Journal of Personality*, *68*(6), 1127–51.
Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/11130735>
- Wilson, I. B., & Cleary, P. D. (1995). Linking clinical variables with health-related quality of life: A conceptual model of patient outcomes. *Journal of the American Medical Association*, *273*(1), 59–65. doi:10.1001/jama.1995.03520250075037
- Winberg, C., Barnes, V., Ncube, K., & Tshinu, S. (2011). Postgraduate students' experiences in interdisciplinary research studies. *South African Journal of Higher Education*, *25*(5), 1003–1020.
- Wirken, L., van Middendorp, H., Hooghof, C., Rovers, M., Hoitsma, A., Hillbrands, L., & Evers, A. (2015). The course and predictors of health-related quality of life in living kidney donors: A systematic review and meta-analysis. *American Journal of Transplantation*, *15*(12), 3041–3054.
- Wolfensberger, W. (1994). Let's hang up "quality of life" as a hopeless term. In D. Goode (Ed.), *Quality of life for persons with disabilities: International perspectives and issues*. (pp. 285–321). Cambridge: Brookline Books.
- Wolthausen, J., Sternberg, S., Gerloff, C., & May, a. (2009). Are cortical spreading depression and headache in migraine causally linked? *Cephalalgia*, *29*, 244–249.
doi:10.1111/j.1468-2982.2008.01713.x
- Wong, M. L., Chia, K. S., Yam, W. M., Teodoro, G. R., & Lau, K. W. (2004). Willingness to donate blood samples for genetic research: A survey from a community in Singapore. *Clinical Genetics*, *65*(1), 45–51. <http://doi.org/10.1111/j..2004.00192.x>

Wood-Dauphinee, S. (1999). Assessing quality of life in clinical research: from where have we come and where are we going? *Journal of Clinical Epidemiology*, 52(4), 355–63.

Retrieved from <http://www.ncbi.nlm.nih.gov/pubmed/10235176>

World Health Organization. (2012). Headache Disorders. Retrieved from

<http://www.who.int/mediacentre/factsheets/fs277/en/#>

Zainuldin, R., Mackey, M., & Alison, J. (2011). Optimal intensity and type of leg exercise training for people with chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*, 11.

Zaller, N., Nelson, K. E., Ness, P., Wen, G., Bai, X., & Shan, H. (2005). Knowledge, attitude and practice survey regarding blood donation in a Northwestern Chinese city. *Transfusion Medicine*, 15(4), 277–286. <http://doi.org/10.1111/j.0958-7578.2005.00589.x>

Appendix A: Informed Consent Brochure

PARTICIPANT INFORMATION LEAFLET AND INFORMED CONSENT

Migraine in South Africa

You are invited to participate in our research project about migraine in South Africa. There is very little published information about the subject in this country and we would like to increase the knowledge in this field. We hope that this research will help health professionals that deal with patients with migraine to understand the disease better and to develop more effective treatments. The aim of this information leaflet is to help you to decide if you would like to participate in the study. Please read and understand this document before the start of the study. Before you agree to take part in this study you should fully understand what is involved. You should not agree to take part unless you are completely happy about what is expected of you. If you have any questions, do not hesitate to ask us. If at any time you may be suffering from any of the symptoms mentioned or if you have any medical questions, you are advised to consult your doctor. This is a research project and does not offer any medical care and it is best that you see your health care provider if you have a health problem or medical question.

What is the purpose of this research?

Migraine has been estimated to occur in 15–17% of women and 5% of men. The aim of this research is to describe the prevalence of migraine headaches in South Africa and to understand the psychological and genetic make-up of the South Africans suffering from the disorder.

WHAT WILL YOU BE ASKED TO DO IF YOU DECIDE TO PARTICIPATE?

The study is made up of *two* parts. In the first part you are asked to fill out a questionnaire. The completion of the questionnaire may take about 40 minutes. The questionnaire begins with a few questions about you (such as your name and age). Although these questions are personal, please be assured that we will not use this information to judge you. You can therefore *feel free to be honest*. The next part of the questionnaire focuses on headache symptoms you may experience. These are followed by some questions about the pain you experience from your migraine. Finally, there is a list of questions about how you react in situations.

The questionnaire must be handed to the researcher along with this *signed consent form* once you have completed it. Please remember that you *do have to put your name on the* questionnaire. The only people that have access to the questionnaires are the principal researcher and the database administrator, who has signed a confidentiality agreement. Once you have completed the form, the principal researcher (Ms Catherine Govender) will assign a unique code to your questionnaire. Your name and unique code will be recorded in a list to which only Ms Govender will have access. We will handle your information in the strictest confidence and will make sure that the information is kept safe.

Once you have handed in your paperwork, we will take a few months to analyse the information from all the people that are participating in the study. Ms Govender will then contact some participants (and you may be one of them) to supply some blood. If you are contacted to donate blood and you are willing to assist, you will need to do the following:

Ms Govender will advise you of the nearest Ampath Pathologist practice in your area.

You will choose a day that is most convenient for your testing. It is important that you have your tests done only if you have been without a headache for seven consecutive days. If you are taking any medication (chronic or acute) in the week leading up to your tests, you will need to provide Ms Govender with a list of these.

You will need to fast for eight to ten hours before your blood is drawn (some people find it best not to eat or drink after 22:00 and then to go to Ampath early the next day. If you choose to do this, please make sure of the opening time of the Ampath in your area)

At Ampath you will be asked to complete some paperwork. The laboratory will know that this is for a research project, but if they ask, just remind them.

The qualified staff will draw your blood. Remember that we are running six tests and collecting an extra vial for genetic testing. Please read further for a description of the aim of the tests. In total we will be drawing 55ml of blood. Just to put this into perspective, when you donate blood, 500ml is taken.

Please remember that the investigator retains the right to withdraw you from the study if it is considered to be *in your best interest*. Please also remember that it is very important to be honest and follow the guidelines and the regulations of the research. If, for any reason, you are unable to follow the instructions, please let us know.

WHY DO THE RESEARCHERS WANT TO KNOW PERSONAL THINGS ABOUT YOU?

We would like to try and understand which groups of people (according to different criteria such as age, ethnicity and medical history) suffer from migraine. By considering all these factors, we may be able to understand how migraines affect people.

WHAT WILL HAPPEN TO THE BLOOD THAT YOU GIVE US?

We will send the blood to a laboratory to be processed and stored. When the sample is sent to the laboratory it will be labelled with your unique code, the location you were in when it was collected and the date of collection.

We will run the following tests:

- Complete blood count: This is a group of tests in which the number of various blood cells are counted. This can tell us if you have certain diseases such as anaemia (a lack of red blood cells).
- Fasting glucose: A test such as this is able to detect abnormal blood sugar levels such as those seen in diabetes
- Lipid profile: We will be able to tell how much cholesterol you have.
- Prothrombin time and International Normalized Ratio: (PT and INR) and Partial thrombin time (PTT): These two tests will tell us if you have any clotting problems
- Neurotransmitter ELISA: these tests are done to measure how much of the neurotransmitters are in your blood. Some of your blood will be used for genetic testing. Over the next 1-5 years we will do the following with your blood sample:
 - Use a technique to measure the expression of a neurotransmitter transporter
 - Put all the data in a confidential scientific database;
 - Study the genetic variation data from all the samples; and
 - Compare individual samples and samples from different ethnic or geographic groups.

We may not use all of your blood in this study. Any blood that is not used will be destroyed once the results have been satisfactorily achieved.

WHAT ARE THE COSTS INVOLVED?

Neither you, nor your medical aid will be required to pay for the assessments carried out. You will also not receive any gifts or payment for participating in this study. Some of the research done with your samples or the information in the scientific databases may eventually lead to the development of new predictive or diagnostic tests, medicines, or other commercial products. If this happens, there is no plan to provide you with any of the profits from those products, or any discounts on or special access to the products.

ARE THERE RISKS INVOLVED IN THIS RESEARCH?

Some people may be uncomfortable about the types of questions asked. Please remember that we are not here to judge you and we request only that you be honest in your answers. You are welcome to let the researcher know about your discomfort with certain questions and may decline to answer, but please remember that this *will influence the accuracy* of our results.

Drawing blood can be uncomfortable and may cause bruising. Some people become dizzy or faint from the process. However, the people that will draw your blood are trained to do so and will take the necessary precautions to cause you as little discomfort as possible and to comply with best practice standards. If you have any kind of bleeding problems, we ask that you rather not participate. Your health and safety are very important to us.

WHO WILL HAVE ACCESS TO MY INFORMATION?

As mentioned, once you have filled in the questionnaire, you will be allocated a unique code. Only the principal researcher will have access to the master list that shows your name and code. Any processing of your information (e.g. recording your answers) will be done using this code and not your real name. This is to protect your privacy and ensure your anonymity.

All identifying information obtained during the study will be treated as strictly confidential. Any data that we share with our colleagues in the scientific world will not contain your identifying details. Data that may be reported in scientific forums (such as journals) will not include any information that identifies you as a participant in this study. We will not sell/give your information to a third party. We may use your test results for future studies.

All information obtained during the course of this research is strictly *confidential*. Data that may be reported in, for instance, scientific journals will not include any information which identifies you as a participant in this research. In connection with this research, it might be important for domestic and foreign *regulatory health authorities* and the College of Agricultural and Environmental Sciences Ethics Committee, University of South Africa, as well as your personal health care providers, to be able to review your records pertaining to this research. Any information uncovered regarding your test results or state of health as a result of your participation in this research will be held in strict confidence. You will be informed of any finding of importance to your health or continued participation in this research via your doctor, but this information will not be disclosed to any other party - in addition to the ones mentioned above - without your written

permission. The only exception to this rule will be cases in which a law exists compelling us to report individuals infected with communicable diseases. In this case, you will be informed of our intent to disclose such information to the authorized state agency.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS RESEARCH?

Your participation in this research is entirely voluntary and you can refuse to participate or stop at any time without stating any reason. Your withdrawal will not affect your access to health care. Should you wish to stop participating, please make contact with the research team and ask for a 'Withdrawal of Consent' form. You will have to fill the form in and send it back to us.

HAS THE RESEARCH RECEIVED ETHICAL APPROVAL?

This protocol was submitted to the Department of Psychology Ethics Committee, University of South Africa and written approval has been granted by that committee. The study has been structured in accordance with the Declaration of Helsinki (last update: 2008), which guides biomedical research involving human/subjects. A copy of the Declaration may be obtained from the investigator should you wish to review it.

WHY MUST I GIVE MY DOCTOR'S NAME?

We feel that it is our duty to report *potentially serious problems* picked up in your laboratory tests. By law, this information may not be communicated directly to you by the laboratory. The information therefore must be sent to your doctor. Your doctor will then communicate this information to you.

PLEASE REMEMBER THAT IF YOU SIGN BELOW, YOU ARE AGREEING TO:

Give blood

Have your DNA sequenced

Complete the necessary questionnaires

If you have any queries, please contact our principal researcher:

Name	Telephone	Postal address	Fax	E-mail
Catherine Govender	+27 12 4296189	Department of Psychology, PO Box 392, Unisa, 0003	+27 12 429 3414	govenco@unisa.ac.za

INFORMED CONSENT FOR THE PROJECT ENTITLED: MIGRAINE IN SOUTH AFRICA

PLEASE COMPLETE THIS IF YOU CONSENT TO PARTICIPATE Please note that this information will not be used by the investigator to break confidentiality. Should the investigator need to contact you, however, these details will be necessary. **Please inform the investigator of any changes to these contact details.**

Full name: _____

Telephone number (work): _____

Cellular phone number or after hours contact number: _____

E-mail address: _____

Your doctor's name: _____ Your doctor's telephone number: _____

Your doctor's address: _____

I hereby confirm that I have been informed about the nature, conduct, benefits and risks of the study. I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the investigation. I am aware that the results of the research, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a research report. I may, at any stage, without prejudice, withdraw my consent and participation in the research. I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the research.

Participant's name _____ Participant's signature _____ Date _____

(Please print)

Witness's name _____ Witness's signature _____ Date _____

(Please print)

VERBAL PARTICIPANT INFORMED CONSENT (APPLICABLE WHEN PARTICIPANT CANNOT READ OR WRITE)

The undersigned investigator has read and explained fully to the participant and/or his/her relative, the participant information leaflet, which has indicated the nature and purpose of the research in which I have asked the participant to participate. The explanation I have given has mentioned both the possible risks and benefits of the research and the alternative treatments available for his/her illness. The participant indicated that he/she understands that he/she will be free to withdraw from the research at any time for any reason and without jeopardizing his/her subsequent injury attributable to the drug(s) used in the research, to which he/she agrees. I hereby certify that the participant has agreed to participate in this research.

Participant's Name _____

(Please print)

Investigator's Name _____ Investigator's Signature _____ Date ____

(Please print)

Witness's Name _____ Witness's Signature _____ Date ____

(Please print)

Please return this signed consent form *and* your answer sheet to the investigator. Thank you for your time!

Appendix B: Clearances

9 October 2013

ETHICAL CLEARANCE OF A RESEARCH PROJECT INVOLVING HUMAN PARTICIPANTS

Project: Psychosocial and Gene Expression Correlates of Quality of Life in Migraine without Aura

Researcher: Catherine Govender

Supervisor: Professor J Elander (Psychology Department, University of Derby, UK)

The proposal was evaluated for adherence to appropriate standards in respect of ethics as required by the Psychology Department of Unisa. The application was approved by the departmental Ethics Committee on the condition that all medical or biomedical procedures will be carried out under appropriate medical supervision



Prof P Kruger

*Coordinator: Ethics Committee
Department of Psychology
College of Human Sciences
University of South Africa*

The items for this thesis are not available because of copyright requirements. For more information, please consult the sections on the relevant questionnaires.