SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

2785.

MAGYAR MÁTÉ

Klinikai neurológiai kutatások
című program

Programvezető: Dr. Kovács Tibor, egyetemi docens

Témavezetők: Dr. Juhász Gabriella, egyetemi docens

Dr. Ertsey Csaba, egyetemi docens

QUALITY OF LIFE AND PERSONALITY TRAITS IN MIGRAINE AND MEDICATION OVERUSE HEADACHE

PhD thesis

Máté Magyar

János Szentágothai Doctoral School of Neurosciences

Semmelweis University

Supervisor: Gabriella Juhász, MD, D.Sc.
Csaba Ertsey, MD, Ph.D.

Official reviewers: Gábor Csukly, MD, Ph.D.
Délia Szok, MD, Ph.D.

Head of the Final Examination Committee: Mária Judit Molnár, MD., D.Sc.

Members of the Final Examination Committee: Ágnes Herczegfalvi, MD, Ph.D.
Ildikó Vastagh, MD, Ph.D.

Budapest

2022

TABLE OF CONTENTS

List of abbreviations

5-HT: 5-hydroxytryptamine

5-HT1B: 5-hydroxytryptamine receptor 1B

5-HT1D: 5-hydroxytryptamine receptor 1D

BFI: The Big Five Inventory

BPPV: benign paroxysmal positional vertigo

CDH: chronic daily headache

CHQQ: Comprehensive Headache-Related Quality of life Questionnaire

DEP: lifetime depression

DLPFC: dorsolateral prefrontal cortex

DMN: default mode network

HADS: Hospital Anxiety and Depression Scale

HRQoL: Health-Related Quality of Life

ICHD-3: International Classification of Headache Disorders, Third Edition

MOH: medication overuse headache

MSQ2.1: Migraine-specific Quality of Life Questionnaire

NSAID: Non-Steroidal Anti-Inflammatory Drug

QoL: quality of life

SD: standard deviation

SF-36: Medical Outcome Survey 36-item Short-Form Health Survey

sig.: significance probability

VAS: Visual Analog Scale

$\chi 2$: chi-squared

1. Introduction

1.1. Epidemiology of migraine and medication overuse headache

Epidemiology is an essential starting point in understanding the burden of disease in the population either in Hungary or worldwide. Incidence and prevalence are widely used measures of disease frequency. Incidence quantifies the number of new events or cases of a disease that develop in a population over a defined period. Prevalence is the proportion of a population that has the disease over a given period (1).

Migraine is a disabling neurovascular disorder, presenting with recurrent episodes of unilateral, moderate to severe headache attacks lasting 4 to 72 hours, associated with phono-, and/or photophobia, nausea, and vomiting (2). Migraine with aura and migraine without aura are the two major types of migraines. Migraine with aura is characterized by transient focal neurological symptoms that usually precede the headache, while migraine without aura is a clinical syndrome characterized by headache with specific features and associated symptoms (2). Migraine is one of the most common pain disorders (3), affecting approximately 11% of the general population (4). The one-year prevalence of migraine without aura was 7.6% (male/female ratio 1:3), and migraine with aura was 2% (female/male ratio 2:1) in a population-based epidemiological survey in Hungary (5). Lipton and colleagues found the one-year prevalence of migraine to be 17.2% in females and 6.0% in males, with the highest prevalence between the ages of 30 and 49 years, the most productive years of life (6). Despite the increasing number of consultations among migraine sufferers over the last 15 years in the United States, migraine remains underdiagnosed and undertreated (6-8). Lipton and colleagues in 2002 found, that only 48% of migraine sufferers had seen a doctor for headaches within the last year, while 21% had not, and 31% had never visited a doctor for headaches (6). The 5-year incidence of migraine was reported to be 8.4%, (female 12.0%, male 3.2%) (9), with a peak between the ages of 20 and 24 years among females and between the ages of 10 and 14 years among males (10).

Medication overuse headache (MOH) is a “headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute or symptomatic headache medication (on 10 or more, or 15 or more days/month, depending on the medication) for more than 3 months.

It usually, but not invariably, resolves after the overuse is stopped.", as described by the International Classification of Headache Disorders, Third Edition (ICHD-3) (2). MOH usually occurs in patients with migraines or tension-type headaches (11). Triptans are among the most common causes of MOH in the western world, with a mean critical duration of overuse of 1.7 years, which is 2.7 years in the case of ergotamine and 4.8 years for simple analgesics (12). No specific, population-based studies are available in the literature about the incidence of MOH yet. Katsarava and colleagues (13) found that the one-year incidence of chronic migraine among episodic migraineurs (n=532) was 14%, with a higher risk for subjects taking greater amounts of analgesics and having higher headache frequency at baseline. MOH prevalence in the general population ranges from 1% to 2%, with a 3:1 female preponderance, affecting the patients most commonly in midlife (14, 15). Bigal and colleagues (16) reported that approximately 60% of the patients in tertiary headache centers in England had transformed migraine with analgesic overuse.

1.2. Quality of life

"Quality of life (QoL) is a concept which aims to capture the well-being, whether of a population or individual, regarding both positive and negative elements within the entirety of their existence at a specific point in time. For example, common facets of QoL include personal health (physical, mental, and spiritual), relationships, education status, work environment, social status, wealth, a sense of security and safety, freedom, autonomy in decision-making, social-belonging and their physical surroundings" (17). The doctor's evaluation of the effect of illness can be different from the patient's perspective; thus, measuring the quality of life (QoL) is important and can give a unique insight into the patient's condition (18).

In medical practice, several outcome measures can be used to describe the patient's condition. These outcome measures can be objective, for example, can be observed by an investigator (e.g., tremor, nystagmus), or can be reproducibly measured by appropriate methods (e.g., lab results, blood pressure). Other outcome measures are subjective and based on the patient's assessment (e.g., mood, pain severity, sleep quality, or quantity). Studying QoL as a subjective indicator is an established means of assessing the burden of headaches from the perspective of the headache sufferers. Objective indicators (which

are not dependent on any input from the patient) are not available in the field of headache research, as headache is a subjective experience. To overcome this problem, numerous standardized endpoints have been developed, such as the Visual Analog Scale (VAS), which consists of a horizontal line, labelled 'No pain' and 'Maximum pain' at opposite ends. Patients are instructed to regard the VAS as a continuum and to indicate their current level of pain along the line between two endpoints. The VAS has previously been shown to be a useful measure for evaluating the efficacy of anti-migraine drugs (19). Paper-based and electronic headache diaries have also been developed and used in clinical trials and everyday medical practice. The most commonly used indicators (headache severity, headache days, and analgesic consumption) are all reported by the patients, lately increasingly supplemented by other subjective indicators, such as Quality of Life (QoL), disability, or headache impact.

The concept of health-related quality of life (HRQoL) and its determinants have evolved since the 1980s to encompass those aspects of overall quality of life that can be clearly shown to affect health — either physical or mental (20, 21). "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO definition of Health) (22). Assessing HRQoL by a detailed patient interview, be the most accurate, is not practical for several reasons, including issues regarding the reproducibility and comparability of data, feasibility, and examiner burden. As HRQoL has gained popularity as an outcome measure in both clinical practice and research for both somatic and mental conditions (23), many HRQoL questionnaires have been developed to overcome the above difficulties. There are two basic types of HRQoL questionnaires: generic and disease-specific questionnaires. The main advantage of using such scales in addition to clinical rating scales is the patient's reflection on their health, which often differs considerably from clinicians' or even carers' views (24).

Generic HRQoL questionnaires, such as Medical Outcome Survey 36-item Short-Form Health Survey (SF-36) (25), measure overall HRQoL, including questions that represent those aspects of health that are important for the majority of people, for example, limitations of physical and/or social activities and vitality (26). Thus, these instruments allow a comparison between the impact of one illness and that of others, and also with the values of healthy individuals. They can measure the effect of various healthcare interventions and can therefore be helpful, among others, in analyzing cost

efficiency or planning resource allocation in health economics studies. Generic instruments may, however, be unresponsive to changes in specific conditions (27).

Disease-specific HRQoL questionnaires, such as the Migraine-specific Quality of Life Questionnaire (MSQ2.1) (28), focus on problems associated with states of a single disease and allow comparisons among illnesses that share the leading symptoms. They can help select the most appropriate therapy for the patient and monitor its efficiency. Moreover, they may better reflect the particular impact of a given condition (27). On the other hand, these questionnaires are not suitable for making a comparison between the impacts of different conditions and different symptomatology.

It has been demonstrated that migraineurs have lower HRQoL, measured by SF-36 (29) and Short Form (SF)-12 (30), compared to the general non-migraine population, but only a small number of studies have investigated the association between HRQoL and headache characteristics. These studies reported that increased migraine severity (indexed by the combination of migraine frequency and pain intensity) (29), lower patient age (31), and higher headache frequency (31, 32) were related to decreased HRQoL in migraineurs. Interestingly, chronic migraine sufferers can have impaired visual QoL, similarly to individuals suffering from other neurological conditions, such as multiple sclerosis, myasthenia gravis, and ischemic neuropathy (33). Furthermore, migraine and depression independently cause decrement in HRQoL, and their comorbidity is well-established (30). Other comorbidities, such as asthma and chronic musculoskeletal pain, further reduce HRQoL in migraineurs (32).

In the U.S. and Europe, several population-based studies have found significantly lower HRQoL in migraineurs compared to an age-matched control population (34-36). Patients with transformed migraine (more than 15 headache days per month) had lower SF-36 scores than patients with chronic tension-type headaches (37) and lower HRQoL than migraine patients with less than 15 headache days per month (38). Other studies have also reported lower scores in migraine patients with increased attack frequency. This suggests that the impact of headaches on HRQoL of the patients is influenced by headache chronicity (39). The majority of migraineurs postpone their household duties and cancel social and family activities because of migraine attacks (40), bringing significant disruption to family life, with an impact on children, spouses and, friends (41, 42).

Before the introduction of the term “chronic migraine”, chronic daily headache (CDH) was an umbrella term for a heterogeneous group of headache disorders (including symptomatic analgesic overuse) characterized by a headache occurring on 15 or more days per month, for more than 3 months (43, 44), with an overall prevalence of 3-5% (45, 46). In a previous study, CDH subjects with analgesic overuse showed lower scores across all SF-36 domains (only physical functioning [p=0.008] and bodily pain [p=0.045] were significant) than CDH subjects without analgesic overuse (47). Another study reported that CDH with analgesic overuse itself induced a meaningful decrease across all domains of SF-36, with physical functioning and bodily pain being the most affected items compared to healthy subjects (48). In a pilot study, patients with MOHs had significantly lower scores across all domains of SF-36 (except physical functioning) compared to the normally expected scores (49).

Previous studies have reported that migraine patients with increased attack frequency had lower HRQoL scores, suggesting that the impact of headaches on HRQoL is influenced by headache chronicity (39). In addition, patients with MOHs had significantly impaired QoL scores measured by SF-36 as compared to patients with episodic migraines (50). However, no research has yet examined the effect of headache features on HRQoL measured by CHQQ among migraineurs and patients with MOHs.

1.3. Neuropsychiatric aspects of migraine

Migraines frequently co-occur with other neuropsychiatric disorders, one of which is depression. On the other hand, approximately half of the patients with major depressive disorder also report coexisting severe headaches, mostly migraines (51, 52). Clinically, not only migraine but also other pain symptoms and syndromes show a higher prevalence in depressed patients, which means that pain can be considered a symptom of depression (53, 54). Conversely, recurring migraine attacks may increase the risk of depression (55). A bidirectional relationship has been suggested between migraine and depression, mutually increasing the risk of each other (55, 56). Shared genetic risk factors can partly explain the co-occurrence of migraine and depression (57), but the exact mechanism is not well understood yet (52). Migraine and anxious depression are partly influenced by overlapping genetic and non-shared environmental factors (58). Anxiety, depression, and migraine are affected by the same biological pathways, for example, the serotonergic and

dopaminergic systems (59, 60), suggesting that disturbances in these systems may increase the risk of these disorders (58). Patients with comorbid migraine and major depression show a significantly higher number of depressive episodes and a significantly higher prevalence of seasonal variation (61). Also, affective temperaments and irritability can be observed (61).

1.4. Neuropsychiatric aspects of medication overuse headache

A significantly larger percentage of individuals with CDH showed clinical depression, measured by the Zung self-rating depression scale, compared to individuals with episodic migraine (62). Psychiatric disorders (e.g., major depressive disorder, generalized anxiety disorder, panic disorder, social phobia, substance-related disorders) significantly more often occurred before the transformation of migraine into MOH than afterward (63). Subjects with MOHs had a greater risk of suffering from depression and anxiety; these disorders, thus, may be risk factors for the evolution of migraine into MOH (63). Individuals with MOHs also have a higher risk of suffering from substance-related disorders than individuals with migraines, which could be explained by the hypothesis that identifies MOH as a part of the spectrum of addictive disorders (63). Mitsikostas and Thomas (64) compared the clinical profile of individuals with primary headache disorders with age- and sex-matched healthy subjects, and they found that anxiety and depressive symptoms were more severe or frequent in individuals with primary headaches and individuals with drug-abuse headaches. Migraineurs with aura had the highest risk for dysthymia and major depression.

1.5. Personality factors in migraineurs and individuals with medication overuse headache

What are the basic dimensions of personality on which individuals differ and that influence their emotional, interpersonal, experimental, attitudinal, and motivational styles? Independent sets of researchers discovered and defined five broad personality traits based on empirical, data-driven research. Raymond Christal and Ernest Tupes developed the initial model based on work at the U.S. Air Force Personnel Laboratory in the late 1950s (65). Digman advanced his five-factor model of personality in 1992 (66), which was extended by Goldberg in 1993 (67). Personality traits reflect basic dimensions

on which people differ. Brent and colleagues emphasized the influence of personality traits on important life outcomes, highlighting the need to more routinely incorporate measures of personality into the QoL questionnaires and encourage further research about the process by which personality traits influence diverse life outcomes (68).

The Big Five Inventory (BFI-44) is one of the questionnaires which measures five factors of personality: extraversion, agreeableness, conscientiousness, neuroticism, and openness (69). Neuroticism includes negative emotions, for example, depression and anxiety, commonly defined as emotional instability. Agreeableness defines the level of cooperativeness and compassion. Extraversion describes the individual's positive emotions, such as a tendency to seek out stimulation and sociability. Conscientiousness refers to organizational ability and carefulness. Openness describes the individual's imagination and intellectual curiosity (70). The stability coefficient of personality traits is from moderate to high both in men and women, with the highest gender-equal stability for openness to experience and the lowest for conscientiousness (71). Neuroticism remains rather stable in middle and older adulthood, with some apparent increase in late life (72).

It was shown as early as the 1980s that neuroticism significantly improved in the clinically improved migraineurs who received biofeedback therapy but not in those who received medication therapy (73). This suggests that the psycho-neurotic characteristics in individuals with migraines may not be attributable to the pain experience but may rather be an inherent feature of migraine etiology (73). Neuroticism might be causally implicated in the development of migraine in young adult women but not in men of similar age (9). Higher neuroticism scores have been found in individuals with migraines compared to individuals with tension-type headaches (74) and healthy subjects (75) and shown a positive correlation with headache duration (number of hours per week) (75). Migraineurs reported themselves to be more irritable, less calm, and less able to relax, compared to control individuals (75). On the other hand, neuroticism appears to be a risk factor not only for migraine (76) but also for major depressive disorder (77). High neuroticism scores and low extraversion, conscientiousness, and openness to experience are significant predictors of depression (78). A higher proportion of individuals with chronic daily headaches have shown abnormal personality profiles (hypochondriasis, depression, hysteria – so-called neurotic triad) than individuals with episodic migraine

(62). In a recent study, female individuals with MOHs have shown significantly lower extraversion, openness, and conscientiousness scores, compared to female individuals with migraines, while male subjects have shown no significant differences (79). Of note, patients with severe untreated anxiety, depression, personality disorders, or other pain comorbidities, which might also influence the personality data, were excluded.

In summary, although neuroticism is a common risk factor for migraine and depression and their co-occurrence, much less is known about the effect of other personality traits on the comorbidity of migraine and depression, whether they have a possible protective role against migraine in depressed patients or vice versa.

2. Objectives

2.1. Study 1

Depression and migraine frequently co-occur as comorbid conditions (55, 56). In migraineurs, a different constellation of personality traits has been described (76, 80), but less attention was paid to personality differences between migraine subjects with and without depression. We hypothesized that not only neuroticism but other personality factors may play an important role in the comorbidity of migraine and depression. Thus, our first study aimed to investigate possible differences in big five personality traits among patients with and without lifetime depression (DEP) who suffered from migraine in the previous 3 months. Recruitment was conducted in a large European population sample in Budapest and Manchester.

2.1.1. Specific aims

- To replicate previous findings about migraine being more prevalent in subjects with DEP than in non-depressed people.
- To determine what other personality factors influence the co-occurrence of migraine and DEP besides neuroticism.
- To investigate migraine specificity of our hypothesis by testing it in non-migraine headache sufferers and subjects with other pain disorders.

2.2. Study 2

Previous research using generic and disease-specific instruments has reported that both migraine (29, 36) and MOH (81) had a diminishing effect on patients' HRQoL. On the other hand, only a few studies have investigated the possible association between HRQoL and headache features. They have reported that increased migraine severity (indexed by the combination of migraine pain intensity and frequency) (29), longer disease duration (31), and higher headache frequency (31, 32) were related to decreased HRQoL in subjects with migraines. Based on these observations, we hypothesized that different aspects of headache characteristics have a significant effect on HRQoL and its domains. We also hypothesized that these effects are more pronounced in MOH compared to migraine patients. Thus, our second study aimed to assess HRQoL differences in subjects with migraines and subjects with MOHs and to observe the effect of certain headache features, namely, headache type (migraine/MOH), headache pain severity, headache frequency, number of years with headaches, aura symptoms, and triptan use on HRQoL.

2.2.1. Specific aims

- To replicate findings according to which patients with MOHs have worse quality of life than migraineurs.
- To investigate the effect of different headache characteristics on HRQoL in migraine and MOH patients.
- To determine whether different domains of HRQoL are similarly affected by headache characteristics.

3. Methods:

3.1. Study 1: Decreased openness to experience is associated with migraine-type headaches in subjects with lifetime depression

The first study was part of an EU-funded research program called NewMood (New Molecules in mood Disorders) and aimed to investigate novel pathomechanisms of major depression and its comorbid disorders, such as anxiety and migraine (82). Participants were recruited from Budapest, Hungary, and Greater Manchester, UK, by contacting general practices and using advertisements (university advertisements, the NewMood website, and newspapers). All willing participants filled out the NewMood booklet containing brief standard and validated questionnaires. Altogether 1,139 subjects responded in Budapest and 2,004 in Manchester by sending back the signed written informed consent and the postal questionnaires. Only subjects with properly completed questionnaires were included in this first study, regardless of ethnicity and reported psychiatric or medical disorders. The final sample consisted of 1,056 participants from Budapest (mean age = 31.40 years) and 1,970 participants from Manchester (mean age = 33.50 years). The study was approved by local ethics committees and carried out in accordance with the Declaration of Helsinki.

Background details (e.g., sex, age), medical history (including psychiatric disorders and reported migraine), and information on socioeconomic status were collected by a brief standard background questionnaire, Hungarian and English versions, respectively. Subject-reported DEP episodes were derived from a set of questions already validated in a subset of participants during face-to-face interviews (83). A background questionnaire was used to determine other pain disorders. The answers were coded “yes” if the subjects did not report migraine but reported at least one of the following conditions: rheumatoid arthritis (n = 31), back pain (n = 162), abdominal pain (n = 43, e.g., Crohn’s disease, ulcerative colitis, irritable bowel syndrome, heartburn), joint pain (n = 16, e.g., arthritis, osteoarthritis), diffuse pain (n = 14, e.g., myalgic encephalomyelitis, complex regional pain, fibromyalgia), or other pain (n = 4, e.g., mastitis, chronic sinusitis).

A migraine-specific validated screening tool, the ID-migraine questionnaire (84, 85) was used to identify subjects with migraine headaches. Participants were considered migraineurs (migraine(ID)) if they experienced at least two out of the following symptoms: photophobia, nausea, and disability during headaches in the previous

3 months (84). Those experiencing one or none of the above symptoms (therefore not fulfilling the criteria for migraine(ID) were considered patients with non-migraine headaches.

We measured five factors of personality (extraversion, agreeableness, conscientiousness, neuroticism, and openness) with the BFI-44 (69). Items were rated on a 5-point Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree). Regarding personality factors, continuous weighted dimension scores (sum of the item scores divided by the number of items completed) were calculated for the analysis.

Statistical analyses were carried out in SPSS 21.0 for Windows (IBM). Pearson's chi-squared test was used to calculate the difference of migraine(ID), non-migraine headaches, and pain prevalence between participants with and without DEP. Multivariate ANOVA was used to investigate the interaction effect of migraine(ID) and DEP on personality factors in the total population (Budapest and Manchester together). Test of between-subject effects and Wilk's lambda statistics were reported. Using a univariate ANOVA post hoc test, we determined the significant interaction effects in the subpopulations to establish replicable findings. We also tested whether the significant interaction was migraine-specific or applicable to non-migraine headaches or other pain. Sex and age were included as covariates in all analyses. The study site was added as an independent factor in population-wise analyses to control for cohort differences. A logistic regression model was constructed to test the effect of sex, age, the five personality factors, DEP, and any significant interaction between personality and DEP on migraine(ID). All statistical testing adopted a two-tailed $p = 0.05$ threshold.

3.2. Study 2.: A cross-sectional study on the quality of life in migraine and medication overuse headache in a Hungarian sample: understanding the effect of headache characteristics

The study was part of a research program conducted in the Headache Center of the Department of Neurology at Semmelweis University and part of the Hungarian Brain Research Program at Semmelweis University. Between 2015 and 2019, altogether 334 subjects were recruited (in the clinical group, migraine: 198, MOH: 50; in the research group, migraine: 71, MOH: 15) from the headache center, referred to as clinical group, and by advertisements (university advertisements and newspapers), referred to as

research group. In the clinical group, no exclusion criteria were applied, while in the research group, exclusion criteria were as follows: current or past serious medical, major psychiatric or neurologic disorders, the use of daily medication except contraceptives, and in the case of migraine patients, the use of preventive medications. Episodic migraine and MOH patients were diagnosed by neurologists and filled out the Comprehensive Headache-related Quality of life Questionnaire (CHQQ). Migraine and MOH patients were eligible if they fulfilled the diagnostic criteria of ICHD-III (Beta) (86) of migraine and MOH, with or without aura symptoms in both groups.

Demographic data (e.g., sex, age) and the following clinical features were assessed by a background questionnaire during the clinical examination: age at migraine onset, number of years with migraines, migraine frequency (average number of migraine days per month), presence of aura symptoms (yes/no), painkiller usage, and migraine severity, which was assessed by visual analog scale (VAS).

The CHQQ is a 23-item headache-specific QoL questionnaire developed and validated by the Headache Research Group at the Department of Neurology at Semmelweis University (87, 88). It is intended to assess headache patients' QoL in detail, covering the previous four weeks. Responders used a 5-point Likert scale to answer questions like "How much did your headaches bother you in your free time (reading, listening to music, hobby, etc.)?" or "How much did the headache interfere with your work activity?", ranging from absolute freedom from restriction (not bother at all) to a maximum restriction (made it impossible). After that, the values were transformed to a 0-100-point scale, where the full restriction is equal to 0, and the absolute absence of restriction is equal to 100. Physical, mental, and social dimensions and the total score were calculated without weighting the item scores (87, 88). The CHQQ is a validated instrument in Hungarian and Serbian and is currently under validation in English to study episodic- and chronic migraines and tension-type headaches. In the current study, CHQQ was used to measure the HRQoL of the participants, and the domain scores were scaled from 0%=worst to 100%=best health/ability/function in accordance with the original scoring of the CHQQ.

Statistical analyses were performed with the statistical software package IBM SPSS 21.0 for Windows (IBM). Based on skewness and kurtosis, the data showed a normal

distribution; therefore, we used parametric tests (independent samples t-test, chi-squared test, and linear regression with enter method). Having 4 multiple regression models, we set the significance threshold to $p \leq 0.0125$ (0.05/4) to correct for multiple testing and to avoid Type I error. Otherwise, all statistical testing adopted a two-tailed $p < 0.05$ threshold.

4. Results

4.1. Study 1.: Decreased openness to experience is associated with migraine-type headaches in subjects with lifetime depression (89)

4.1.1. Phenotypes and demographic characteristic

A total of 3026 willing participants from Budapest and Manchester filled out the NewMood booklet, which contained short standard and validated questionnaires. In total, n=1139 subjects in Budapest and n=2004 in Manchester responded by returning the postal questionnaires and the signed written informed consent form. Only subjects with properly completed questionnaires were included in this study, regardless of ethnicity and reported medical or psychiatric disorders. The demographic characteristics of the studied populations are displayed in Table 1.

Table 1. Characteristics of the participants in the first study (89)

	Total population	**Manchester**	**Budapest**
Demographics			
Participant number (n)	3026	1970 (65%)	1056 (35%)
Female (n, %)	2082 (69%)	1341 (68%)	741 (70%)
Age (mean SE)	32.8 (0.19)	33.5 (0.23)	31.4 (0.33)
Migraine, headache, and pain			
Migraine(ID) (n, %)	829 (27%)	586 (30%)	243 (23%)
Proportion of Migraine(ID) without / with lifetime depression (n, %)	353 (20%) / 476 (38%)	190 (20%) / 396 (39%)	163 (20%) / 80 (35%)
Non-migraine headache (n, %)	1380 (46%)	838 (43%)	542 (51%)
Other pain disorders	239 (8%)	139 (7%)	100 (10%)

Table 1. (continued) Characteristics of the participants in the first study (89)

Psychometric measures	Total population	Manchester	Budapest
Reported lifetime depression (n, %)	1246 (41%)	1016 (52%)	230 (22%)
BFI-44 neuroticism (mean SE)	3.15 (0.02)	3.32 (0.02)	2.83 (0.03)
BFI-44 extraversion (mean SE)	3.29 (0.02)	3.15 (0.02)	3.55 (0.03)
BFI-44 conscientiousness (mean SE)	3.67 (0.01)	3.65 (0.02)	3.70 (0.02)
BFI-44 agreeableness (mean SE)	3.76 (0.01)	3.75 (0.01)	3.78 (0.02)
BFI-44 openness (mean SE)	3.74 (0.01)	3.63 (0.01)	3.94 (0.02)

Note: SE: standard error of mean, ID: data derived from the ID-migraine questionnaire; BFI-44: Big Five Inventory.

4.1.2. Association of migraine and lifetime depression with personality factors

Patients with DEP reported significantly more migraine(ID) (DEP: 38% vs. no-DEP: 20%, Pearson chi^2=124.4, df=1, p<0.001) in line with the scientific literature (90, 91), and more other pain disorders (DEP: 10% vs. no-DEP: 7%, Pearson chi^2=11.3, df=1, p=0.001) but less non-migraine headaches (DEP: 40% vs. no-DEP: 50%, Pearson chi^2=27.9, df=1, p<0.001). After controlling for study site, age, and sex, the results of MANOVA revealed the main effects of both migraine(ID) and DEP (Table 2A) and their interaction effect on personality dimensions (Table 2B).

Table 2. MANOVA on personality factors to investigate the effect of lifetime depression and migraine(ID) in the total population

Table 2A. Multivariate test Wilks' Lambda indicated that lifetime depression and migraine significantly interact with personality factors (89)

Effect	F	df	p-value
intercept	*3008.795*	*5, 3012*	<0.001
sex	*67.179*	*5, 3012*	<0.001
age	*35.914*	*5, 3012*	<0.001
DEP	*72.458*	*5, 3012*	<0.001
Migraine(ID)	*12.999*	*5, 3012*	<0.001
cohort	*37.163*	*5, 3012*	<0.001
DEP * Migraine(ID)	*3.213*	*5, 3012*	0.007
DEP * cohort	*8.080*	*5, 3012*	<0.001
Migraine(ID) * cohort	0.425	5, 3012	0.831
DEP * Migraine(ID) * cohort	0.682	5, 3012	0.637

Note: ID: data derived from the ID-migraine questionnaire, DEP: lifetime depression; cohort: Budapest versus Manchester

Table 2B. Univariate ANOVA post hoc results by the five personality factors in case of significant MANOVA Wilks' Lambda (89)

		Total population		Manchester		Budapest	
Effect	Personality factor	F	p-value	F	p-value	F	p-value
sex	extraversion	*11.240*	0.001	*11.579*	0.001	0.982	0.322
	agreeableness	*60.904*	<0.001	*43.036*	<0.001	*18.521*	<0.001
	conscientiousness	*37.718*	<0.001	*24.583*	<0.001	*13.446*	<0.001
	neuroticism	*80.292*	<0.001	*48.447*	<0.001	*31.707*	<0.001
	openness	*19.421*	<0.001	*34.230*	<0.001	0.279	0.597
age	extraversion	*6.689*	0.010	2.237	0.135	*5.415*	0.020
	agreeableness	*42.611*	<0.001	*42.056*	<0.001	*4.690*	0.031
	conscientiousness	*130.075*	<0.001	*94.455*	<0.001	*36.904*	<0.001
	neuroticism	*13.461*	<0.001	*12.200*	<0.001	2.255	0.133
	openness	*5.265*	0.022	*4.430*	0.035	1.175	0.279
DEP	extraversion	*77.908*	<0.001	*82.655*	<0.001	*22.569*	<0.001
	agreeableness	*37.760*	<0.001	*25.970*	<0.001	*18.186*	<0.001
	conscientiousness	*73.671*	<0.001	*61.861*	<0.001	*27.943*	<0.001
	neuroticism	*341.452*	<0.001	*498.703*	<0.001	*58.369*	<0.001
	openness	2.232	0.135	1.097	0.295	1.120	0.290
Migraine (ID)	extraversion	*11.452*	0.001	*5.573*	0.018	*6.356*	0.012
	agreeableness	*7.507*	0.006	*4.285*	0.039	3.715	0.054
	conscientiousness	1.515	0.219	1.868	0.172	0.289	0.591
	neuroticism	*62.933*	<0.001	*41.385*	<0.001	*27.375*	<0.001
	openness	0.572	0.450	0.111	0.739	1.533	0.216

Table 2B.(continued) Univariate ANOVA post hoc results by the five personality factors in case of significant MANOVA Wilks' Lambda (89)

		Total population		Manchester		Budapest	
Effect	Personality factor	F	p-value	F	p-value	F	p-value
cohort	extraversion	*43.509*	<0.001				
	agreeableness	0.810	0.368				
	conscientiousness	0.299	0.585				
	neuroticism	*73.189*	<0.001				
	openness	*103.784*	<0.001				
DEP * migraine (ID)	extraversion	0.005	0.945	0.080	0.777	0.068	0.795
	agreeableness	2.264	0.133	*5.092*	0.024	0.120	0.729
	conscientiousness	0.000	0.991	0.368	0.544	0.191	0.662
	neuroticism	1.651	0.199	0.854	0.356	0.883	0.348
	openness	*10.653*	0.001	*4.759*	0.029	*6.467*	0.011
DEP * cohort	extraversion	1.070	0.301				
	agreeableness	0.471	0.493				
	conscientiousness	0.000	0.987				
	neuroticism	*29.631*	<0.001				
	openness	0.001	0.981				

Note: ID: data derived from the ID-migraine questionnaire, DEP: lifetime depression; cohort: Budapest versus Manchester

Test of between-subject effect indicated that DEP and non-DEP subjects differed significantly in agreeableness, extraversion, neuroticism, and contentiousness. Subjects with or without migraine(ID) significantly diverged on neuroticism, extraversion, and agreeableness. Only one personality factor, openness, was affected by the interaction between DEP and migraine(ID) (Figure 1.). Significant DEP and migraine(ID) interaction effect on openness was found in both the Budapest (F=6.467, df=1,1050 p=0.011) and the Manchester cohort using post hoc univariate ANOVA (F=4.759, df=1,1970,

p=0.029). Lower openness to experience scores were observed in DEP + migraine(ID) individuals compared to individuals without migraine(ID) and/or DEP.

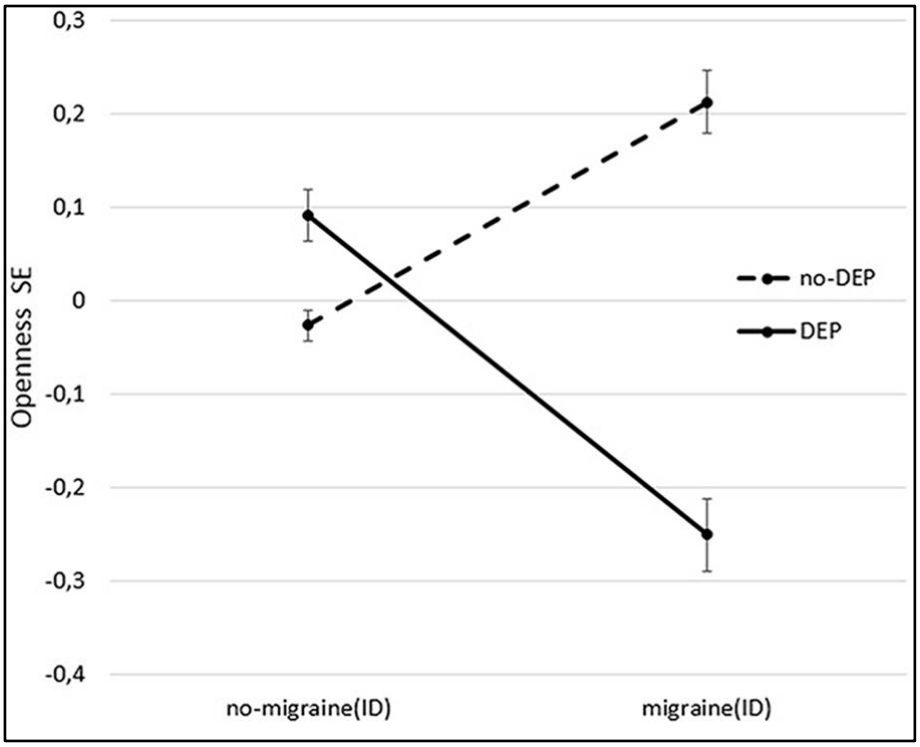

Figure 1. Significant interaction effect of lifetime depression and migraine(ID) on openness (89)

The figure shows standardized openness to experience scores (BFI-44) and standard error of means (SE). Subjects with migraine(ID) without DEP had the highest openness to experience scores. **Note:** DEP: lifetime depression reported; no-DEP: no lifetime depression reported

4.1.3. Association of non-migraine headaches, migraine(ID) and lifetime depression with personality factors

After categorizing headaches into non-migraine headaches and migraine(ID), a similar interaction effect was demonstrated between headaches and DEP on openness (F=6.107, df=2,3012, p=0.002, Figure 2.) across the whole study population (after correction for age, sex, and study site). The difference between non-DEP and DEP patients was significant in those who did not have headaches in the past 3 months (F=3.867, df=1,811, p=0.05) and in the migraine(ID) group (F=7.160, df=1,823,

p=0.008), but the non-migraine headache group did not show significant difference (F=0.392, df=1,1374, p=0.532) in openness.

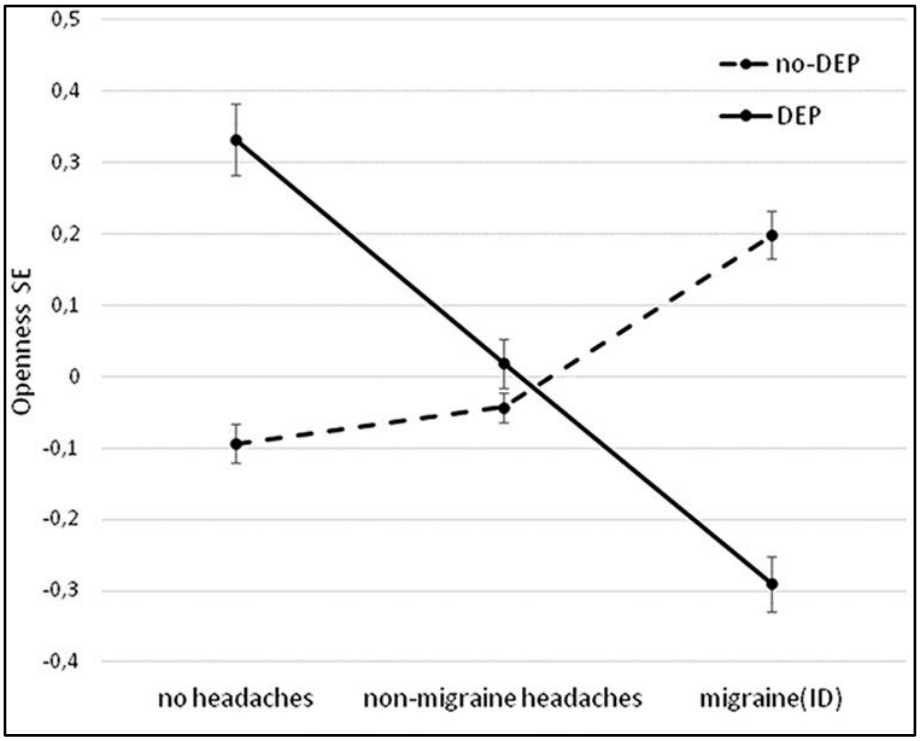

Figure 2. Significant interaction effect of lifetime depression and headaches on openness in the total population (89)

The figure shows standardized openness to experience scores (BFI-44) and standard error of means (SE). The difference between DEP and non-DEP subjects was significant in subjects without headaches in the past 3 months and in the migraine(ID) group but not in the non-migraine headache group. **Note:** DEP: lifetime depression reported; no-DEP: no lifetime depression reported.

4.1.4. Effect of other pain disorders and lifetime depression on personality factors

No significant interaction was found between DEP and other pain disorders (F=0.490, df=1,3016, p=0.484) on openness.

4.1.5. Factors influencing migraine risk based on the above results

Logistic regression analysis revealed that, by taking into account sex, age, cohort, DEP, personality factors, and DEP by openness interaction, four variables increase migraine(ID) risk: neuroticism, openness, DEP, and sex. In addition, after controlling for all the above variables, DEP by openness interaction still significantly reduced the odds ratio for migraine(ID) (Table 3.). Furthermore, in contrast to previous results, our data demonstrated that openness to experience increased in subjects with migraine(ID), but higher openness scores were present only in migraine(ID) patients without DEP. Based on our results, openness to experience may prevent the co-occurrence of depression and migraine. Interestingly, a similar effect could not be demonstrated in the case of non-migraine headaches or other pain disorders, suggesting that openness may represent a specific protective mechanism toward the comorbidity of migraine and depression.

Table 3. Logistic regression on migraine(ID) adding sex, age, cohort, personality factors, lifetime depression, and lifetime depression by openness interaction (89)

Variables	OR	95% CI for OR		Wald	df	p-value
		Lower	Upper			
sex	*1.95*	*1.58*	*2.42*	*37.55*	*1*	<0.001
age	1.00	0.99	1.00	1.12	1	0.290
cohort	1.03	0.84	1.25	0.07	1	0.796
extraversion	0.97	0.87	1.09	0.22	1	0.642
agreeableness	1.02	0.88	1.19	0.10	1	0.753
contentiousness	1.05	0.92	1.19	0.54	1	0.463
neuroticism	*1.68*	*1.47*	*1.91*	*60.49*	*1*	<0.001
openness	*1.32*	*1.07*	*1.62*	*6.93*	*1*	0.008
DEP	*4.95*	*1.79*	*13.68*	*9.52*	*1*	0.002
DEP by openness	*0.73*	*0.56*	*0.95*	*5.49*	*1*	0.019
Constant	*0.01*			*51.43*	*1*	<0.001

After controlling for all variables, DEP by openness to experience still significantly decreased the odds ratio for migraine(ID). **Note:** OR: Odds Ratio; CI: confidence interval; DEP: lifetime depression.

4.2. Study 2.: A cross-sectional study on quality of life in migraine and medication overuse headache in a Hungarian sample: understanding the effect of headache characteristics (92)

4.2.1. Phenotypes and demographic characteristics

A total of 334 willing participants were examined by neurologists and completed the CHQQ. 269 subjects had migraines, and 65 subjects had MOHs. The demographic characteristics of the population and the statistical comparison of the migraine and MOH subgroups are presented in Table 4. MOH patients were significantly older than migraine sufferers and reported a significantly higher headache frequency in the previous month. Headache pain severity measured by VAS was approximately equal in the MOH and migraine groups without significant difference in number of years with headaches. There was no significant difference in the distribution of patients with or without triptan use, with or without aura, and whether they belong to the research or clinical group. 97.8% of patients with migraines used at least one type of painkiller, while, all MOH patients used painkillers, so we did not use this variable in a further analysis examining predictors of QoL (see Table 4.) Of the total study population, 71.3% used non-steroidal anti-inflammatory drugs NSAIDs, 23.7% used combined analgesics, 18% used triptans, and 13.5% used at least two types of painkillers. MOH patients had lower physical, mental, social, and total CHQQ scores compared to migraine patients. After pairwise comparisons without covariates, the differences above remained significant in all dimensions except the social subscale (see Table 4.).

Table 4. Demographic data and statistical comparison of the migraine and MOH subgroups in our second study (92)

	Total population (N=334)	**Migraine (N=269)**	**MOH (N=65)**	**Test statistic (t/χ^2)**	**Effect size (Cohen's d)**
Female (n, %)	288 (86.2%)	235 (87.4%)	53 (81.5%)	χ^2: 1.494	-
Age (mean, SD)	35.57 (11.89)	34.03 (10.85)	41.98 (13.81)	t: 4.334**	0.69
Number of years with headaches (mean, SD)	13.77 (11.20)	13.23 (10.16)	16.00 (14.62)	t: 1.452	0.25
Headache frequency (mean, SD)	9.90 (9.66)	6.56 (6.85)	23.71 (7.01)	t: 17.773**	2.49
Headache pain severity (VAS, mean, SD)	53.87 (28.29)	54.25 (28.19)	52.29 (28.90)	t: 0.492	0.07
Aura (n, %)	yes: 44 (13.2%)	yes: 37 (13.8%)	yes: 7 (10.8%)	χ^2: 0.408	-
Painkillers	yes: 328 (98.2%)	yes: 263 (97.8%)	yes: 65 (100%)	χ^2: 1.476	-
Triptan use (n, %)	yes: 60 (18%)	yes: 46 (17.1%)	yes: 14 (21.5%)	χ^2: 0.700	-
Recruitment method	clinical: 248 (74.3%) research: 86 (25.7%)	clinical: 198 (73.6%) research: 71 (26.4%)	clinical: 50 (76.9%) research: 15 (23.1%)	χ^2: 0.301	-

Table 4. (continued) Demographic data and statistical comparison of the migraine and MOH subgroups in our second study (92)

	Total population	**Migraine**	**MOH**	**Independent Samples Test (t-test)/chi-squared test**	**Effect size (Cohen's d)**
CHQQ Physical (mean, SD)	41.19 (17.88)	42.05 (18.44)	37.59 (14.93)	t: 2.085*	0.25
CHQQ Mental (mean, SD)	47.65 (16.72)	48.72 (16.83)	43.23 (15.59)	t: 2.505*	0.33
CHQQ Social (mean, SD)	48.14 (21.60)	49.11 (22.03)	44.15 (19.36)	t: 1.801	0.23
CHQQ Total (mean, SD)	45.51 (16.09)	46.48 (16.39)	41.47 (14.20)	t: 2.475*	0.31

Note: MOH: medication overuse headache, SD: standard deviation, CHQQ: Comprehensive Headache-related Quality of life Questionnaire VAS: visual analogue scale. * $p < 0.05$, ** $p<0.001$

4.2.2. Relationship between QoL and headache-related variables

To explain physical, mental, social, and total CHQQ scores in the total population, we used the following explanatory variables: age, sex, recruitment method (clinical/research subgroup affiliation), number of years with headaches, headache type (migraine/MOH), aura symptoms, triptan use, headache frequency, and headache pain severity. The results are presented in Table 5. Across the study population, the regression models explained 22.0% of social, 20.3% of physical, and 19.6% of total score variance, while only 11.1% variance of mental subscale was explained by the models.

Better physical QoL was associated with younger age, research subsample status, no triptan use, and less severe headache pain after correction for multiple testing. Higher mental subscale scores were associated with no triptan use. Better social QoL was related to no triptan use and research subsample status. Regarding the total score, a significant

association was found with triptan use, the method of recruitment, and headache pain severity.

After controlling for demographic and other headache characteristics, headache type was not a significant explanatory variable for any CHQQ subscale. Less severe headache pain and no triptan use were the most consistently associated variables with higher CHQQ scores.

Table 5. Standardized regression weights between health-related quality of life and demographic and headache-related variables (92)

	Physical headache-related QoL		**Mental headache-related QoL**		**Social headache-related QoL**		**CHQQ total**	
	stand. beta	**p-value**	**stand. beta**	**p-value**	**stand. beta**	**p-value**	**stand. beta**	**p-value.**
Sex (male / female)	*-0.114*	*0.023*	-0.091	0.086	-0.054	0.27	*-0.101*	*0.045*
Age	**-0.182**	**0.005**	-0.100	0.15	-0.085	0.19	*-0.140*	*0.032*
Clinical / research subsample	**0.286**	**<0.001**	0.082	0.17	**0.322**	**0.001**	**0.241**	**0.001**
Headache type (migraine / MOH)	-0.051	0.48	0.006	0.94	-0.016	0.83	-0.022	0.77
Headache years	0.056	0.34	0.088	0.16	-0.060	0.30	0.044	0.46
Aura (yes/no)	0.054	0.30	0.074	0.18	*0.125*	*0.016*	0.091	0.085
Triptan use (yes/no)	**0.163**	**0.002**	**0.171**	**0.002**	**0.160**	**0.002**	**0.187**	**0.001**

Table 5. (continued) Standardized regression weights between health-related quality of life and demographic and headache-related variables (92)

	Physical headache-related QoL		**Mental headache-related QoL**		**Social headache-related QoL**		**CHQQ total**	
	stand. beta	**p-value**	**stand. beta**	**p-value**	**stand. beta**	**p-value**	**stand. beta**	**p-value.**
Headache pain severity (VAS)	**-0.166**	**0.001**	*-0.128*	*0.017*	*-0.122*	*0.015*	**-0.158**	**0.002**
Headache frequency	-0.004	0.95	*-0.171*	*0.041*	-0.059	0.46	-0.096	0.23
R^2/Adjusted R^2	**0.203/0.180**		**0.111/0.086**		**0.220/0.198**		**0.196/0.174**	

Across all CHQQ domains, the most consistent predictors of HRQoL were triptan use, headache pain severity, and recruitment method. MOH alone was not a predictor of worse HRQoL. **Note:** MOH: medication overuse headache, CHQQ: Comprehensive Headache-related Quality of life Questionnaire, VAS: visual analog scale, stand. beta: standardized beta coefficient, in bold: significant results after correction for multiple testing, in italic: nominally significant results.

4.2.3. Post hoc test of the effect of triptan use on headache characteristics and CHQQ scores

Considering the finding that triptan use was a consistent predictor of all CHQQ subscales, we tested the relationship of triptan use to other headache descriptors and QoL. Our results showed that triptan users have significantly more years with headache and poorer QoL on all subscales and the total scale. Headache pain severity and headache frequency were independent of triptan use (Table 6.).

Table 6. Differences in headache frequency, number of years with headaches, headache pain severity, and quality of life scores between triptan users (N=60) and non-users (N=274) (92)

		Mean (SD)	Test statistics (t)	Effect size (Cohen's d)
Headache frequency	Triptan users	9.33 (7.54)	0.602	0.07
	Triptan non-users	10.03 (10.08)		
Number of years with headaches	Triptan users	18.03 (13.18)	2.862*	0.41
	Non-triptan users	12.83 (10.52)		
Headache pain severity (VAS)	Triptan users	50.35 (33.52)	0.927	0.15
	Non-triptan users	54.64 (27.02)		
CHQQ Physical	Triptan users	35.10 (15.63)	3.230*	0.42
	Non-triptan users	42.52 (18.09)		
CHQQ Mental	Triptan users	42.17 (15.07)	3.044*	0.40
	Non-triptan users	48.85 (16.85)		
CHQQ Social	Triptan users	40.92 (20.18)	3.023*	0.41
	Non-triptan users	49.73 (21.61)		
CHQQ Total	Triptan users	39.44 (13.45)	3.704**	0.46
	Non-triptan users	46.84 (16.34)		

Triptan users have significantly more years with headaches and worse QoL on all CHQQ subscales and total scale. **Note:** SD: standard deviation, CHQQ: VAS: visual analog scale, Comprehensive Headache-related Quality of life Questionnaire, *$p<0.01$, **$p<0.001$

5. Discussion

5.1. Study 1

The results of our first study of a large European sample are consistent with the previous literature, supporting that DEP and migraine are often comorbid conditions, and both neuroticism and DEP independently increase the risk of migraine. Furthermore, in contrast with previous findings, our data showed that openness is an independent risk factor for migraine(ID), but higher openness to experience is present only in migraine sufferers who do not have DEP. Thus, as a new finding, openness may prevent the co-occurrence of depression and migraine. Interestingly, a similar protective effect could not be demonstrated in mixed or other headaches or other pain disorders, suggesting that openness might represent a specific protective mechanism against migraine and depression.

5.1.1. Openness to experience in health and diseases

Consistent with previous studies (76, 77), neuroticism appears to be a risk factor for both migraine(ID) and DEP in our population study. However, in contrast to previous studies (93, 94), we showed that openness also increases the risk of migraine. We found an interaction effect between DEP and migraine in the case of openness to experience, indicating higher openness scores only in migraine(ID) patients without depression. Openness is a distinctive constellation of affective and cognitive styles, including curiosity, creativity, flexible thinking, increased receptiveness for salient stimuli, preference for new experiences, and absorption in sensory experience (95, 96). Although openness to experience is the most controversial trait in the 5-factor model (97, 98), recent studies have found it to be an important factor in coping with various disorders, as it plays a protective role against depression (78). Similarly, openness may help to counteract the depressogenic effects of somatic conditions, such as hemodialysis (99) or the postpartum period (100). Furthermore, openness to experience has been found to be associated with higher physiological adaptation and lower physiological reactivity to recurrent social evaluative stress, as measured by blood pressure, heart rate, and respiratory rhythm changes, suggesting that this personality trait might be a protective factor against harmful effects of stress (101). Consistent with our results, migraineurs with higher openness

scores are more creative and flexible in the management of their condition, which, in turn, reduces the impact of migraine on their daily life, leading to less functional impairment (102). This effect is particularly important in the comorbidity of migraine and depression, as they have already been reported to have a specific relationship reflected in their high comorbidity. Consistent with our findings, this relationship differs from the ones between depression and other types of headaches (55, 103).

5.1.2. Specific relationship between migraine and depression

Our study supports previous findings suggesting a positive association between migraine and depression. DEP, however, has the opposite effect on non-migraine headaches. In a 2-year follow-up study, pre-existing migraine increased the risk of developing depression 5.8-fold, and pre-existing depression increased the risk of developing migraine 3.4-fold (55). Also, current anxiety and depression have been associated with a greater increase in migraine risk compared to other types of headaches and pain disorders (103). This specific relationship between migraine and depression, but not other types of headaches, may indicate a common neurobiological or genetic element in the pathophysiology of depression and migraine, as previously suggested (91, 104).

The nature of the relationship between depression and painful conditions in general is not well understood yet. Several factors may play a role in the increased co-occurrence of depression and migraine. There may be a direct causal relationship, although the direction is unclear. Depression could contribute to an increased sensitivity to pain, or migraine could lead to depression through recurring pain and resulting reduced QoL (58) or through learned helplessness due to its unpredictable nature. Depression may also occur as a side-effect and a neurobiological consequence of migraine-associated pain. Another possibility is that depression and migraine are different symptomatic manifestations of the same underlying syndrome (58). Recent studies have shown that shared environmental and pleiotropic genetic influences may also be responsible for the increased comorbidity between migraine and depression, including the involvement of shared biological pathways, such as the serotonergic and dopaminergic pathways and stress as a major risk factor for both disorders (58).

5.1.3. Possible mechanism of openness as a protective factor in the co-occurrence of migraine and depression

The roughly 50% heritability of the Big Five traits reflects a strong biological background (105). Less neurobiological explanations are available in the case of openness compared to other traits, such as extraversion or neuroticism (97). A higher-order solution for the 5-factor model has been proposed by several authors, with two superfactors, namely, stability (including neuroticism, conscientiousness, and agreeableness) in relation to the variation in serotonergic function and plasticity (including openness to experience and extraversion) in relation to the variation in dopaminergic function (106, 107). The exploratory tendency on a more abstract, cognitive, and motivational level is a key characteristic of openness (97). The novelty-associated rewarding stimuli are modulated by the dopaminergic system (97, 108, 109), which may regulate both cognitive and motivational aspects of openness (97).

Previous studies have shown that openness appears to be associated with anterior cingulate and prefrontal dopaminergic projections (97, 108). A recent study demonstrated a positive association between openness and functional connectivity between the right DLPFC and the right ventral tegmental area/substantia nigra of the midbrain, which is the chief source of dopaminergic inputs during resting-state and various tasks (95). Robust association between neurocognitive tasks reflecting DLPFC function and openness but not extraversion supports the specific relationship between dopaminergic regulation in the DLPFC and openness (97). DLPFC plays a unique role in both depression and migraine; therefore, DLPFC could be a key mediator of the protective effect of openness on the co-occurrence of depression and migraine. Increased vulnerability to depression in the presence of negative stimuli is associated with decreased DLPFC activity (110). Furthermore, it has been hypothesized that the DLPFC exhibits constant upregulation to enhance descending pain modulation (111, 112).

During an experimental pain-induction task, cognitive pain processing areas, such as the DLPFC, showed increased activation in patients with migraines interictally, suggesting that the DLPFC has an important role in the top-down control of pain in migraine (113). Studies examining cognitive control of pain in migraine patients demonstrated a chronic DLPFC engagement in migraine, which was independent of the

pain condition (pain or no-pain) and similarly modulated by cognitive tasks across all conditions (111).

In addition, pain catastrophizing in migraineurs has been associated with reduced cortical grey matter volume in areas including the DLPFC (114).

Openness in migraine might be a sign of enhanced DLPFC activity that provides not only a more efficient frontal top-down control on pain (112, 115) and other negative stimuli (116) but is also associated with flexible processing of novel salient information, which represent a better adaptation strategy to everyday life and less depression. In addition, openness in healthy controls has indicated a more efficient resting-state brain network activity (117). Interestingly, alterations in the resting-state brain networks, especially in the default mode network (DMN), are characteristics of both depression (118) and migraine (119). Thus, a better DMN integrity in migraineurs with higher openness might contribute to a diminished risk for depression.

5.1.4. Therapeutic consequences of increased openness

Depression comorbid with other somatic disorders has been shown to be an independent predictor of poor treatment outcome (120). A recent study of a large sample of episodic migraineurs has shown that comorbid depression worsens the responsiveness to acute migraine treatment (121). Understanding the neurobiological background of this particularly high and specific comorbidity between migraine and depression may improve our treatment strategies. The fact that openness to experience has been associated with increased response to placebo analgesia in migraine sufferers (122) and better response to both psycho- and pharmacotherapy in depressed individuals (123) further underscores the importance of earlier findings. Moreover, both the intensity and frequency of migraine attacks and depressive symptoms have been significantly reduced by deep transcranial magnetic stimulation of the DLPFC (124).

5.1.5. Limitations

As a limitation, we cannot draw any conclusions about the causal relationship between migraine, depression, and openness, due to our cross-sectional design. In addition, assessment of both pain and headache and DEP was based on self-report. The use of the ID-migraine questionnaire, which covers only the previous 3 months, increased

the risk of classifying some migraineurs with less frequent, lifelong migraine into the non-migraine group. However, it is important to emphasize that the ID-migraine questionnaire is a valid screening tool for migraine with good specificity and sensitivity (84, 125). Despite similar recruitment strategies, the prevalence of depression was higher in the Manchester cohort than in the Budapest cohort. However, the proportion of migraine(ID) in the with and without DEP subgroups was very similar in both cohorts, and the significant interaction effect of DEP and migraine(ID) on openness was replicated in both cohorts. Further studies with longitudinal design and clinical samples would be necessary to reveal the importance of openness either in neural activity or daily life.

5.2. Study 2

In our second study, triptan use was associated with lower CHQQ scores on all subscales. Headache pain severity assessed with VAS was associated with lower physical and total CHQQ scores after controlling for age, sex, recruitment method, and other headache-related factors, such as headache type, number of years with headaches, headache frequency, and aura symptoms. 19.6%-22.0% of the variance in total CHQQ scores and subscales (physical and social subscales) was explained by the above-mentioned parameters examined together, except for the mental subscale with which only 11.1% of the variance was associated. Interestingly, the headache type itself, namely, migraine or MOH, was not a significant predictor of any CHQQ subscales in our study population after considering other headache characteristics, while recruitment strategy, i.e., clinical versus research subsample, gained importance as a significant predictor of the social, physical, and total CHQQ scores.

5.2.1. The most consistent factors associated with all HRQoL domains

Interestingly, triptan use was associated with lower scores on all CHQQ subscales, while headache pain severity was associated with lower scores on the physical and total CHQQ subscales.

Triptans are the most commonly used medications for acute migraines, acting as serotonin 1B (5-HT_{1B}) and 1D (5-HT_{1D}) receptor agonists (126). Despite their relatively common use, the relationship between triptan therapy and HRQoL has rarely been investigated.

In a recent study, work productivity and HRQoL were significantly impaired in insufficient triptan responders compared to triptan responders (127). In our study population, triptan use was associated with poor QoL, but, interestingly, headache frequency and headache pain severity did not differ significantly between triptan users and non-users. However, triptan users had significantly more years with headaches than non-users. A possible explanation is that triptan use is a surrogate marker for migraine sufferers with longer disease duration, as previously suggested (25, 128), but our results cannot be fully explained by this relationship. Taking into account other headache-related variables, including the number of years with headaches, triptan use was still consistently associated with different aspects of HRQoL measured by CHQQ. An explanation for the

association between HRQoL and triptan use could be that patients experiencing a greater burden of headache and lower HRQoL prefer to use triptans. Another explanation is that, although triptans are effective, QoL can also be affected by the well-known side effects of triptans (fatigue/drowsiness, dizziness, difficulty in thinking, nausea, tachycardia, warmth, muscle weakness, and chest pressure), which are important factors in migraine management and probably significantly impair patient compliance (129). These side effects of triptans were not included in our model. However, it would be important to investigate the role of triptan-induced side effects on HRQoL as well as the HRQoL among users of calcitonin gene-related peptide (CGRP) receptor antagonist second-generation gepants, which constitute a novel group of acute migraine drugs causing less prevalent side effects and rebound headaches (130, 131).

Headache pain severity, namely, headache pain intensity measured by VAS, influenced physical and total CHQQ domains significantly after correcting for other headache-related variables and multiple testing. Our results confirm the findings of a previous study: the HRQoL deteriorated consistently with increasing migraine severity indicated by the combination of migraine frequency and pain intensity (29).

Besides headache-related factors, the recruitment method was another strong predictor of HRQoL variance in our study. Since the main difference between the two cohorts is the exclusion of comorbidities in subjects recruited through advertisements, we assume that comorbidities in the clinical population might explain poorer HRQoL. It is well known that migraine often coexists with other neuropsychiatric disorders, the most common of which is depression. Coexisting severe headaches, in most cases migraine, have also been reported in about half of patients with major depression (90, 91). As for migraine, associations with other psychiatric conditions, such as panic disorder (132) and certain personality traits, such as neuroticism (76), have also been noted. In combination with a variety of mental health disorders, migraine seems to have worse health-related outcomes and HRQoL than migraine alone (133). Despite these findings, the mental health subscale of CHQQ was not significantly impacted by our recruitment strategy. This might imply additional factors, such as physical disorders or complaints, differences in social backgrounds, and other psychological traits, which were not examined in our study but could explain how the recruitment method affected HRQoL. Thus, it is important to emphasize that the results of headache research, including HRQoL measures, may not be

representative of a more diverse real-world clinical sample where comorbidities and other disadvantages are more common.

5.2.2. HRQoL and other headache-related factors

Our study was the first to show a nominally associated negative effect of aura symptoms on the social subscale of CHQQ. So far, no literature has pointed out the difference in HRQoL between migraineurs with and without aura. However, other diseases with transient neurological symptoms, such as benign paroxysmal positional vertigo (BPPV) (134) and Ménière's disease (135), are also associated with significantly poorer QoL. Based on these studies, we hypothesize that transient aura symptoms may impair social activity, promoting poorer HRQoL.

Although affecting mental HRQoL, headache frequency was not a consistent predictor of HRQoL, in contrast to previous studies (31, 32). A positive bidirectional relationship between mood symptoms (as measured by the Hospital Anxiety and Depression Scale (HADS)) and migraine frequency has been reported in a previous study (136). In another study, a higher frequency of migraine attacks (either with or without aura) correlated with higher symptom scores of anxiety and depression (as measured by Beck's Depression Inventory and Hospital Anxiety and Depression Subscales) (137). In fact, this association between depression and migraine has also been supported by genetic findings (138). Interestingly, our variables predicted the lowest variance of the CHQQ mental health subscale, indicating the potential role of other genetic and biological correlates of mental health, which were outside the focus of our research.

5.2.3. Headache type and HRQoL

Contrary to prior studies, headache type was not a significant predictor of any of the subscales after correcting for other predictors, even though all CHQQ subscales (apart from the social one) showed significant differences between migraine and MOH patients when analyzed alone. As part of the Medication Overuse Treatment Strategy trial, a cross-sectional study using the EQ-5D-5L questionnaire to measure QoL among patients with MOHs found lower QoL scores in patients with higher headache frequency for all EQ-5D-5L measures except the self-care scale (139), similarly to our results. An increase in the number of headache-free days among migraineurs with 4 or more headache days per

month was associated with improved HRQoL, as measured by the EuroQol-5D questionnaire (140). However, we could not replicate these findings in our study after controlling for other headache-related factors. In episodic and chronic migraineurs, headache chronicity had both direct and indirect effects on QoL, as measured by MSQ2.1. Interestingly, one of the factors directly contributing to lower QoL was the female sex, but the pathophysiology is still unclear (141). We found similar trends for total and physical CHQQ subscale scores even after adjustment for other headache-related factors. This suggests that HRQoL is more affected by migraine in women than in men. Physical composite scores (PCS) and mental composite scores (MCS) are norm-based scores with higher scores reflecting better HRQoL. In a previous study, both episodic and chronic migraineurs had significantly lower PCS and MCS, compared to patients without migraines, but episodic and chronic migraineurs were not compared to each other (142). Lower MCS and PCS on SF-36 have been observed in patients with increased migraine severity (i.e., frequency and pain intensity), but only MCS showed a significant change (29). This is in line with our findings, namely that higher headache frequency and severity are associated with lower mental CHQQ score after controlling for age, sex, recruitment method, and other headache-related factors. The above-mentioned study did not use each subscale of SF-36 to measure patients' HRQoL but only PCS and MCS. In an earlier study, significantly lower scores on the bodily pain and physical functioning subscales of SF-36 have been observed in a mixed group of chronic migraine, chronic tension-type headache, and new daily persistent headache with analgesic overuse patients (47). Based on previous studies and our findings, it is important to consider headache-related factors in future studies that focus on the effects of migraine and analgesic overuse on HRQoL.

It is important to note that preventive headache medications taken daily to reduce the frequency, duration, and severity of headaches can affect HRQoL. Previous studies have concluded that different types of preventive medications can improve QoL of both episodic and chronic migraine sufferers (143-146), as well as patients with MOHs (147, 148). In the present study, however, we have not evaluated the role of migraine preventive medication in QoL.

5.2.4. Limitations

First, subjects with comorbidities were excluded from the research subsample but not from the clinical subsample. This might have influenced our results. The difference in preventive medication use is another limitation. In the clinical subgroup, preventive headache medication was not an exclusion criterion, but in the research subsample, neither MOH nor migraine patients received headache preventive medication. Additionally, the exact frequency and dose of preventive medications used by the clinical sample were not recorded. Evaluating the difference in HRQoL between patients with and without preventive medication might also be valuable. It is also important to emphasize that MOH develops in patients with a pre-existing primary headache, which is migraine (45) in most of the cases, but can be tension-type headache (45) or cluster headache (149) as well. In our study, 52% of MOH patients had migraines, 14% had pure tension-type headaches, and 34% had both migraine and tension-type headaches before MOH developed. Thus, it is worth considering that pre-existing primary headaches may influence HRQoL in MOH sufferers, which should be further investigated in future studies.

6. Conclusion

Consistent with previous studies, our first study showed that migraine and depression are often comorbid conditions, and both lifetime depression and neuroticism independently increase the risk of migraine. As a new finding, we concluded that, openness to experience is an independent migraine trait, but higher openness is present only in migraine sufferers who do not have lifetime depression, so openness to experience may prevent the co-occurrence of migraine and depression. On the other hand, we could not demonstrate a similar protective effect in the case of other or mixed headaches or other pain disorders, suggesting that openness to experience might represent a specific protective mechanism toward depression in migraine. Our results shed light on distinguishing features of migraine with and without depression with respect to personality traits. These results can help to understand the biopsychosocial background of migraine and pave the way for new strategies for prevention and intervention on both pharmaco- and psychotherapeutic levels to develop personalized treatments.

In our second study, we demonstrated that triptan use and headache pain severity were consistent predictors of HRQoL measured by the CHQQ after controlling for age, sex, recruitment method, and other headache-related factors, such as headache type, aura symptoms, number of years with headaches, and headache frequency. These parameters together explained 19.6%-22.0% of the variance in CHQQ total scores and subscales (physical and social subscales), except the mental subscale in which only 11.1% of the variance was predicted. Interestingly, headache type itself, namely migraine or MOH, was not a significant predictor of any CHQQ subscale in our study population after taking into account other headache characteristics. As a new finding, aura symptoms affected the variance of social HRQoL, which needs further investigation. In line with previous studies, headache frequency influenced the variance of mental scores: migraine frequency had a bidirectional relationship with mood symptoms (136) and a positive correlation with depression and anxiety symptom scores (137). Our results support that it is important to examine not only the headache type itself, but also the impact of different headache characteristics on HRQoL to identify key players in HRQoL deterioration, appropriately treat different patient populations, and guide public health policies in terms of health services utilization and healthcare costs.

In summary, our key findings are:

- We replicated previous findings, namely that migraine and depression are frequently comorbid conditions.
- We observed that both neuroticism and lifetime depression independently increase the risk of migraine.
- As a new finding, we observed that openness to experience may prevent the co-occurrence of migraine and lifetime depression.
- Interestingly, similar protective effects could not be demonstrated in case of mixed or other headache or pain disorders, suggesting that openness to experience might represent a specific protective mechanism toward migraine comorbidity with lifetime depression.
- We replicated that migraineurs and patients with MOHs have different HRQoL scores; more specifically, MOH patients have lower scores.
- We revealed that headache type (migraine or MOH) is not a significant predictor of HRQoL on any CHQQ subscales after considering other headache characteristics.
- Our study demonstrated for the first time that triptan use was a consistent predictor of lower HRQoL on all CHQQ subscales.
- Finally, we observed that recruitment strategy (clinical versus research subsample) is a significant predictor of the social, physical, and total CHQQ scores: the clinical sample had lower HRQoL scores on these subscales.

Synthetizing the original findings, we showed that several factors can influence the well-being of migraine and MOH patients.

We hypothesize that, besides headache features, personality traits can also affect the HRQoL of patients. Level of neuroticism and extraversion are the best predictors of mental health, life satisfaction, and positive affects in the general population (150, 151). Higher neuroticism is associated with lower SF-36 scores (social functioning and role limitations due to emotional problems) (152) and poor QoL. On the other hand, high extraversion and conscientiousness are positively associated with QoL (153). Neuroticism is strongly linked to emotion regulation: neurotic people tend to blame others

and underestimate the progress of goals. Additionally, they have emotion regulation difficulties and low self-efficacy, which can lead them to conclude that life problems are beyond their control. In contrast, conscientious people may have a higher QoL because they are organized, hardworking, and efficient, which likely contributes to their ability to achieve personal goals (153). Extraversion positively affects QoL directly or via self-efficacy beliefs and emotion regulation acting as a mediating factor; thus, individuals who enjoy the company of others may find themselves to be particularly self-effective, which, in turn, can lead them to be more positive about their life and functioning (153). In conclusion, personality traits are significantly associated with HRQoL scores, independently of their relationship to demographic variables and DSM-IV mood and anxiety disorders, suggesting that HRQoL is influenced not only by the disease, current situation, or health status but also by personality traits, which are relatively stable throughout a lifetime (23). Thus, we can hypothesize that not only headache features but also personality trait differences can play a key role in the deterioration of HRQoL in both migraineurs and patients with MOHs. In our second study, subjects in the clinical population, where neuropsychiatric diseases were not exclusion criteria, had lower HRQoL scores than subjects in the research subsample. In our first study, we found that higher openness to experience may be a protective factor in the co-occurrence of migraine and lifetime depression, while higher neuroticism scores can lead to the opposite result. Thus, higher neuroticism and lower openness scores (characteristics of subjects with migraines and lifetime depression in our first study) may be associated with lower HRQoL scores. It can be explained by the differences in coping and emotion regulation strategies resulting from the differences in personality traits. These theories become very complex when we simultaneously consider all personality aspects of interest. It is important to emphasize that in a subgroup of migraineurs, the episodic nature (a few headaches per month) becomes chronic (15 or more headache days/month for more than 3 months, on at least 8 days/month with the features of migraine) (2). The same progression occurs in patients with MOHs on the basis of a primary headache disorder with analgesic overuse (2). Identifying the risk factors predicting these changes, such as comorbid depression and higher neuroticism for migraine, can offer insights into the mechanisms of the disease; therefore, besides providing the optimal pharmacological

treatment for migraine and MOH, it is important to organize complex care programs for these patients.

Based on these findings, it would be useful to design complex headache clinics where not only headache specialists would diagnose and treat migraine, MOH and other headache disorders but also behavioral and clinical psychologists and psychiatrists, consultants from psychosomatic medicine would work together to explore comorbidities, personality factors, HRQoL and evaluate situational constraints (e.g., dealing with a specific event) and individual differences (e.g., financial or health status, genetic risk factors). The headache specialist would be the leading figure in establishing the correct headache diagnosis and developing therapy plans in close collaboration with team members and patients. In an ideal situation, patients should be informed about the diagnosis, potential triggering and aggravating factors, probable comorbidities, and the role of personality factors. Based on the previous literature and our findings, there is a close relationship between depression, neuroticism, and migraine. Consequently, psychologists would have an important role in the evaluation of patients as well as in therapy. Education and self-management should be part of the treatment: lifestyle education, self-management, and giving information about appropriate drug use and the risks of drug overuse. Psychophysiological and cognitive behavioral training are the core methods of this approach (154). Relaxation is often combined with biofeedback, which is an evidence-based therapy for primary headaches and lacks side effects (155, 156). Not only avoidance of headache triggers but also active management and coping strategies should be in focus. Overall, a personalized treatment plan for acute and, if required, prophylactic treatment should be prepared, following the international guidelines. Multidisciplinary care teams should educate patients on how to better handle headaches and improve therapies to reduce headache frequency and severity, thereby enhancing HRQoL. Future studies should further develop the underlying theoretical model, considering the more specific interplay between different personality traits.

7. Summary

Migraine and depression frequently co-occur as comorbid conditions and mutually increase each other's risk. This may be partially influenced by personality factors. Understanding this relationship would be crucial to better understand the contributors to migraine and help identify biological and psychological targets for prevention and intervention. Migraine and MOH cause a deleterious effect on HRQoL, but only a small number of studies have investigated the association between HRQoL and headache features. In our first study, neuroticism proved to be an independent risk factor for both migraine(ID) and lifetime depression, while openness to experience was significantly lower in the co-occurrence of migraine(ID) and lifetime depression, suggesting that increased openness to experience, possibly manifested in advantageous or optimal cognitive processing of pain experience in migraine, may decrease the risk of the co-morbidity of migraine and depression. This finding might provide insight for newer prevention and intervention approaches in the treatment of these frequently co-occurring conditions. In our second study, we demonstrated that headache-related factors significantly but not equally contributed to HRQoL measured by CHQQ. Consequent predictors were triptan use and headache pain severity, while other observed headache features affected the variance only in some CHQQ scales. The identification of factors playing the major role in the deterioration of HRQoL is important to adequately manage different patient populations and guide public health policies. Based on our results, we further hypothesize that, besides headache features, personality traits can also indirectly affect HRQoL, which would be in line with previous studies. Thus, it would be worthwhile to examine not only the clinical characteristics of headaches but also personality traits, situational constraints (e.g., dealing with a specific event) and individual differences (e.g., financial or health status). All these could contribute to the development of personalized treatments and healthcare strategies for subjects with migraines and MOHs.

8. References

1. Scher A, Stewart W, Lipton R. Migraine and headache: a meta-analytic approach. Seattle: WA: IASP Press; 1999. p.159-70.
2. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211.
3. Bigal ME, Lipton RB, Stewart WF. The epidemiology and impact of migraine. Curr Neurol Neurosci Rep. 2004;4(2):98-104.
4. Stovner L, Hagen K, Jensen R, Katsarava Z, Lipton R, Scher A, Steiner TJ, Zwart J-A. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia. 2007;27(3):193-210.
5. Bánk J, Márton S. Hungarian migraine epidemiology. Headache. 2000;40(2):164-9.
6. Lipton RB, Scher AI, Kolodner K, Liberman J, Steiner TJ, Stewart WF. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002;58(6):885-94.
7. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001;41(7):646-57.
8. Lipton RB, Stewart WF, Simon D. Medical consultation for migraine: results from the American Migraine Study. Headache. 1998;38(2):87-96.
9. Breslau N, Chilcoat HD, Andreski P. Further evidence on the link between migraine and neuroticism. Neurology. 1996;47(3):663-7.
10. Stang PE, Yanagihara PA, Swanson JW, Beard CM, O'Fallon WM, Guess HA Melton LJ. Incidence of migraine headache: a population-based study in Olmsted County, Minnesota. Neurology. 1992;42(9):1657-62.
11. Srikiatkhachorn A, le Grand SM, Supornsilpchai W, Storer RJ. Pathophysiology of medication overuse headache--an update. Headache. 2014;54(1):204-10.
12. Limmroth V, Katsarava Z, Fritsche G, Przywara S, Diener HC. Features of medication overuse headache following overuse of different acute headache drugs. Neurology. 2002;59(7):1011-4.

13. Katsarava Z, Schneeweiss S, Kurth T, Kroener U, Fritsche G, Eikermann A, Diener H-C, Limmroth V. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology. 2004;62(5):788-90.

14. Kristoffersen ES, Lundqvist C. Medication-overuse headache: epidemiology, diagnosis and treatment. Ther Adv Drug Saf. 2014;5(2):87-99.

15. Straube A, Pfaffenrath V, Ladwig KH, Meisinger C, Hoffmann W, Fendrich K, Vennemann M, Berger K. Prevalence of chronic migraine and medication overuse headache in Germany--the German DMKG headache study. Cephalalgia. 2010;30(2):207-13.

16. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre--clinical characteristics and treatment outcomes. Cephalalgia. 2004;24(6):483-90.

17. Teoli D, Bhardwaj A. Quality of Life. Treasure Island (FL): In: StatPearls [Internet]; 2022.

18. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? Br J Cancer. 1988;57(1):109-20.

19. Lines CR, Vandormael K, Malbecq W. A comparison of visual analog scale and categorical ratings of headache pain in a randomized controlled clinical trial with migraine patients. Pain. 2001;93(2):185-90.

20. McHorney CA. Health status assessment methods for adults: past accomplishments and future challenges. Annu Rev Public Health. 1999;20:309-35.

21. Moriarty DG, Zack MM, Kobau R. The Centers for Disease Control and Prevention's Healthy Days Measures - population tracking of perceived physical and mental health over time. Health Qual Life Outcomes. 2003;1(37):1-8.

22. World Health Organization. WHO definition of Health. Official Records of the World Health Organization. New York. 1946. p. 100.

23. Straten Av, Cuijpers P, Zuuren FJv, Smits N, Donker M. Personality traits and health-related quality of life in patients with moodand anxiety disorders. Qual Life Res. 2006;16(1):1-8.

24. Ware JE. Conceptualizing and measuring generic health outcomes. Cancer. 1991;67(3):774-9.

25. D'Amico D, Grazzi L, Usai S, Leonardi M, Raggi A. Disability and quality of life in headache: where we are now and where we are heading. Neurol Sci. 2013;34(1):1-5.
26. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30(6):473-83.
27. Guyatt GH, Feeny DH, Patrick DL. Measuring health-related quality of life. Ann Intern Med. 1993;118(8):622-9.
28. Cole JC, Lin P, Rupnow MF. Validation of the Migraine-Specific Quality of Life Questionnaire version 2.1 (MSQ v. 2.1) for patients undergoing prophylactic migraine treatment. Qual Life Res. 2007;16(7):1231-7.
29. Leonardi M, Raggi A, Bussone G, D'Amico D. Health-related Quality of Life, Disability and Severity of Disease in Patients With Migraine Attending to a Specialty Headache Center. Headache. 2010;50(10):1576-86.
30. Lipton RB, Hamelsky SW, Kolodner KB, Steiner TJ, Stewart WF. Migraine, quality of life, and depression. Neurology. 2000;55(5):629-35.
31. AlHarbi FG, AlAteeq MA. Quality of life of migraine patients followed in neurology clinics in Riyadh, Saudi Arabia. J Family Community Med. 2020;27(1):37-45.
32. Terwindt GM, Ferrari MD, Tijhuis M, Groenen SM, Picavet HS, Launer LJ. The impact of migraine on quality of life in the general population: the GEM study. Neurology. 2000;55(5):624-9.
33. Hanson LL, Ahmed Z, Katz BJ, Warner JEA, Crum AV, Zhang Y, Baggaley S, Pippitt K, Cortez MM, Digre BK. Patients With Migraine Have Substantial Reductions in Measures of Visual Quality of Life. Headache. 2018;58(7):1007-13.
34. Launer LJ, Terwindt GM, Ferrari MD. The prevalence and characteristics of migraine in a population-based cohort: the GEM study. Neurology. 1999;53(3):537-42.
35. Gobel H, Petersen-Braun M, Soyka D. The epidemiology of headache in Germany: a nationwide survey of a representative sample on the basis of the headache classification of the International Headache Society. Cephalalgia. 1994;14(2):97-106.
36. Lipton RB, Liberman JN, Kolodner KB, Bigal ME, Dowson A, Stewart WF. Migraine headache disability and health-related quality-of-life: a population-based case-control study from England. Cephalalgia. 2003;23(6):441-50.

37. Wang SJ, Fuh JL, Lu SR, Juang KD. Quality of life differs among headache diagnoses: analysis of SF-36 survey in 901 headache patients. Pain. 2001;89(2-3):285-92.

38. Meletiche DM, Lofland JH, Young WB. Quality-of-life differences between patients with episodic and transformed migraine. Headache. 2001;41(6):573-8.

39. Monzón MJ, Lainez MJ. Quality of life in migraine and chronic daily headache patients. Cephalalgia. 1998;18(9):638-43.

40. Edmeads J, Findlay H, Tugwell P, Pryse-Phillips W, Nelson RF, Murray TJ. Impact of migraine and tension-type headache on life-style, consulting behaviour, and medication use: a Canadian population survey. Can J Neurol Sci. 1993;20(2):131-7.

41. Holmes WF, MacGregor EA, Dodick D. Migraine-related disability: impact and implications for sufferers' lives and clinical issues. Neurology. 2001;56(6):9-13.

42. Smith R. Impact of migraine on the family. Headache. 1998;38(6):423-6.

43. Siberstein SD, Lipton RB, Solomon S, Mathew NT. Classification of daily and near-daily headaches: proposed revisions to the IHS criteria. Headache. 1994;34(1):1-7.

44. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. Neurology. 1996;47(4):871-5.

45. Castillo J, Munoz P, Guitera V, Pascual J. Kaplan Award 1998. Epidemiology of chronic daily headache in the general population. Headache. 1999;39(3):190-6.

46. Lanteri-Minet M, Auray JP, El Hasnaoui A, Dartigues JF, Duru G, Henry P, Lucas C, Pradalier A, Chazot G, Gaudin A-F. Prevalence and description of chronic daily headache in the general population in France. Pain. 2003;102(1-2):143-9.

47. Guitera V, Munoz P, Castillo J, Pascual J. Quality of life in chronic daily headache: a study in a general population. Neurology. 2002;58(7):1062-5.

48. Colas R, Munoz P, Temprano R, Gomez C, Pascual J. Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology. 2004;62(8):1338-42.

49. Benz T, Nüssle A, Lehmann S, Gantenbein AR, Sándor PS, Elfering A, Aeschlimann AG, Angst F. Health and quality of life in patients with medication overuse headache syndrome after standardized inpatient rehabilitation: A cross-sectional pilot study. Medicine (Baltimore). 2017;96(47):84-93.

50. Altintaş E, Karakurum GB, Taşkintuna N, Saritürk Ç. Correlation Between Life Events and Quality of Life in Patients with Medication-Overuse Headache. Noro Psikiyatr Ars. 2015;52(3):233-9.

51. Ligthart L, Penninx BW, Nyholt DR, Distel MA, de Geus EJ, Willemsen G, Smit JH, Boomsma DI. Migraine symptomatology and major depressive disorder. Cephalalgia. 2010;30(9):1073-81.

52. Samaan Z, Farmer A, Craddock N, Jones L, Korszun A, Owen M, McGuffin P. Migraine in recurrent depression: case-control study. Br J Psychiatry. 2009;194(4):350-4.

53. Lépine JP, Briley M. The epidemiology of pain in depression. Hum Psychopharmacol. 2004;19 Suppl 1:S3-7.

54. Stahl SM. Does depression hurt? J Clin Psychiatry. 2002;63(4):273-4.

55. Breslau N, Lipton RB, Stewart WF, Schultz LR, Welch KM. Comorbidity of migraine and depression: investigating potential etiology and prognosis. Neurology. 2003;60(8):1308-12.

56. Breslau N, Schultz LR, Stewart WF, Lipton RB, Lucia VC, Welch KM. Headache and major depression: is the association specific to migraine? Neurology. 2000;54(2):308-13.

57. Merikangas KR, Merikangas JR, Angst J. Headache syndromes and psychiatric disorders: association and familial transmission. J Psychiatr Res. 1993;27(2):197-210.

58. Ligthart L, Nyholt DR, Penninx BW, Boomsma DI. The shared genetics of migraine and anxious depression. Headache. 2010;50(10):1549-60.

59. Breslau N, Andreski P. Migraine, personality, and psychiatric comorbidity. Headache. 1995;35(7):382-26.

60. Frediani F, Villani V. Migraine and depression. Neurol Sci. 2007;28 Suppl 2:S161-5.

61. Oedegaard KJ, Fasmer OB. Is migraine in unipolar depressed patients a bipolar spectrum trait? J Affect Disord. 2005;84(2-3):233-42.

62. Mathew NT, Stubits E, Nigam MP. Transformation of episodic migraine into daily headache: analysis of factors. Headache. 1982;22(2):66-8.

63. Radat F, Creac'h C, Swendsen JD, Lafittau M, Irachabal S, Dousset V, Henry P. Psychiatric comorbidity in the evolution from migraine to medication overuse headache. Cephalalgia. 2005;25(7):519-22.

64. Mitsikostas DD, Thomas AM. Comorbidity of headache and depressive disorders. Cephalalgia. 1999;19(4):211-7.

65. Tupes EC, Christal RE. Recurrent personality factors based on trait ratings. J Pers. 1992;60(2):225-51.

66. Digman JM. Personality Structure: Emergence of the Five-Factor Model. Annual Rev Psychol. 1990;41:417-40.

67. Goldberg LR. The structure of phenotypic personality traits. Am Psychol. 1993;48(1):26-34.

68. Roberts BW, Kuncel NR, Shiner R, Caspi A, Goldberg LR. The Power of Personality: The Comparative Validity of Personality Traits, Socioeconomic Status, and Cognitive Ability for Predicting Important Life Outcomes. Perspect Psychol Sci. 2007;2(4):313-45.

69. John OP, Sanjay S. The Big Five Trait taxonomy: History, measurement, and theoretical perspectives. In: Pervin LA, John OP (eds). *Handbook of personality: Theory and research*. New York: Guilford Press.; 1999. p. 102-39.

70. Power RA, Pluess M. Heritability estimates of the Big Five personality traits based on common genetic variants. Transl Psychiatry. 2015;5(7):1-4.

71. Rantanen J, Metsapelto RL, Feldt T, Pulkkinen L, Kokko K. Long-term stability in the Big Five personality traits in adulthood. Scand J Psychol. 2007;48(6):511-8.

72. Steunenberg B, Twisk JW, Beekman AT, Deeg DJ, Kerkhof AJ. Stability and change of neuroticism in aging. J Gerontol B Psychol Sci Soc Sci. 2005;60(1):27-33.

73. Sovak M, Kunzel M, Sternbach RA, Dalessio DJ. Mechanism of the biofeedback therapy of migraine: volitional manipulation of the psychophysiological background. Headache. 1981;21(3):89-92.

74. Merikangas KR, Stevens DE, Angst J. Headache and personality: results of a community sample of young adults. J Psychiatr Res. 1993;27(2):187-96.

75. Huber D, Henrich G. Personality traits and stress sensitivity in migraine patients. Behav Med. 2003;29(1):4-13.

76. Ligthart L, Boomsma DI. Causes of comorbidity: pleiotropy or causality? Shared genetic and environmental influences on migraine and neuroticism. Twin Res Hum Genet. 2012;15(2):158-65.

77. Kenneth KS, Margaret G, Charles OG, Nancy LP. Personality and Major Depression: A Swedish Longitudinal, Population-Based Twin Study. Arch Gen Psychiatry. 2006;63(10):1113-20.

78. Naragon-Gainey K, Watson D. Consensually defined facets of personality as prospective predictors of change in depression symptoms. Assessment. 2014;21(4):387-403.

79. Mose LS, Pedersen SS, Jensen RH, Gram B. Personality traits in migraine and medication-overuse headache: A comparative study. Acta Neurol Scand. 2019;140(2):116-22.

80. Brandt J, Celentano D, Stewart W, Linet M, Folstein MF. Personality and emotional disorder in a community sample of migraine headache sufferers. Am J Psychiatry. 1990;147(3):303-8.

81. Colas R, Munoz P, Temprano R, Gomez C, Pascual J. Chronic daily headache with analgesic overuse: epidemiology and impact on quality of life. Neurology. 2004;62(8):1338-42.

82. Deakin JF, Harro J, Anderson IM. NewMood: a productive European model of collaboration for translational research in depression. Eur Neuropsychopharmacol. 2011;21(1):1-2.

83. Juhasz G, Dunham JS, McKie S, Thomas E, Downey D, Chase D, Lloyd-Williams K, Toth ZG, Platt H, Mekli K, Payton A, Elliott R, Williams SR, Anderson IM, Deakin JFW. The CREB1-BDNF-NTRK2 pathway in depression: multiple gene-cognition-environment interactions. Biol Psychiatry. 2011;69(8):762-71.

84. Lipton RB, Dodick D, Sadovsky R, Kolodner K, Endicott J, Hettiarachchi J, Harrison W. A self-administered screener for migraine in primary care: The ID Migraine validation study. Neurology. 2003;61(3):375-82.

85. Rapoport AM, Bigal ME. ID-migraine. Neurol Sci. 2004;25 Suppl 3:258-60.

86. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia. 2013;33(9):629-808.

87. Manhalter N, Palasti A, Bozsik G, Afra J, Ertsey C. Examining the psychometric properties of a new quality of life questionnaire in migraineurs. Ideggyogy Sz. 2010;63(9-10):305-13.

88. Manhalter N, Bozsik G, Palásti A, Csépány E, Ertsey C. The validation of a new comprehensive headache-specific quality of life questionnaire. Cephalalgia. 2012;32(9):668-82.

89. Magyar M, Gonda X, Pap D, Edes A, Galambos A, Baksa D, Kocsel N, Szabo E, Bagdy Gy, Elliott R, Kokonyei Gy, Juhasz G. Decreased Openness to Experience Is Associated with Migraine-Type Headaches in Subjects with Lifetime Depression. Front Neurol. 2017;8:270.

90. Ligthart L, Penninx BW, Nyholt DR, Distel MA, de Geus EJ, Willemsen G, Smit JH, Boomsma DI. Migraine symptomatology and major depressive disorder. Cephalalgia. 2010;30(9):1073-81.

91. Samaan Z, Farmer A, Craddock N, Jones L, Korszun A, Owen M, McGuffin P. Migraine in recurrent depression: case-control study. Br J Psychiatry. 2009;194(4):350-4.

92. Magyar M, Kökönyei G, Baksa D, Galambos A, Édes AE, Szabo E, Kocsel N, Gecse K, Dobos D, Gyüre T, Juhász G, Ertsey Cs. A cross-sectional study on the quality of life in migraine and medication overuse headache in a hungarian sample: understanding the effect of headache characteristics. Ideggyogy Sz. 2022;75(7-8):253-63.

93. Mateos V, Garcia-Monco JC, Gomez-Beldarrain M, Armengol-Bertolin S, Larios C. Personality factors, degree of disability and therapeutic management of patients with migraine visiting a neurology unit for the first time (Psicomig study). Rev Neurol. 2011;52(3):131-8.

94. Saunders EF, Nazir R, Kamali M, Ryan KA, Evans S, Langenecker S, Gelenberg AJ, McInnis MG. Gender differences, Clinical Correlates and Longitudinal Outcome of Bipolar Disorder with Co-morbid Migraine. J Clin Psychiatry. 2014;75(5):512-9.

95. Passamonti L, Terracciano A, Riccelli R, Donzuso G, Cerasa A, Vaccaro M, Novellino F, Fera F, Quattrone A. Increased functional connectivity within mesocortical networks in open people. NeuroImage. 2015;104:301-9.

96. McCrae RR, Costa PT. Conceptions and Correlates of Openness to Experience. In: Hogan R, Johnson J, Briggs S, editors. Handbook of Personality Psychology. San Diego: Academic Press; 1997. p. 825-74.
97. DeYoung CG, Peterson JB, Higgins DM. Sources of openness/intellect: cognitive and neuropsychological correlates of the fifth factor of personality. J Pers. 2005;73(4):825-58.
98. Costa PT, McCrae RR. The NEO Personality Inventory. Odessa: Taylor&Francis; 1985. p 223-250.
99. Bugarski V, Sakac V, Vodopivec S, Slankamenac P. Relation between personality dimensions and depressive symptoms in patients on hemodialysis. Med Pregl. 2010;63(5-6):305-12.
100. Imširagić AS, Begić D, Vuković IS, Šimićević L, Javorina T. Multivariate analysis of predictors of depression symptomatology after childbirth. Psychiatr Danub. 2014;26(Suppl 3):416-21.
101. Lu W, Wang Z, Hughes BM. The association between openness and physiological responses to recurrent social stress. Int J Psychophysiol. 2016;106:135-40.
102. Chan JK, Consedine NS. Negative affectivity, emotion regulation, and coping in migraine and probable migraine: a New Zealand case-control study. Int J Behav Med. 2014;21(5):851-60.
103. Ligthart L, Gerrits MM, Boomsma DI, Penninx BW. Anxiety and depression are associated with migraine and pain in general: an investigation of the interrelationships. J Pain. 2013;14(4):363-70.
104. Breslau N, Davis GC, Andreski P. Migraine, psychiatric disorders, and suicide attempts: an epidemiologic study of young adults. Psychiatry Res. 1991;37(1):11-23.
105. Riemann R, Angleitner A, Strelau J. Genetic and environmental influences on personality: A study of twins reared together using the self- and peer-report NEO-FFI scales. J Pers. 1997.;65(3):449-75.
106. Digman JM. Higher-order factors of the Big Five. J Pers Soc Psychol. 1997;73(6):1246-56.
107. DeYoung CG. Higher-order factors of the Big Five in a multi-informant sample. J Pers Soc Psychol. 2006;91(6):1138-51.

108. Depue RA, Collins PF. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. Behav Brain Sci. 1999;22(3):491-517.
109. Waelti P, Dickinson A, Schultz W. Dopamine responses comply with basic assumptions of formal learning theory. Nature. 2001;412(6842):43-8.
110. Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci. 2011;12(8):467-77.
111. Mathur VA, Khan SA, Keaser ML, Hubbard CS, Goyal M, Seminowicz DA. Altered cognition-related brain activity and interactions with acute pain in migraine. Neuroimage Clin. 2015;7:347-58.
112. Seminowicz DA, Shpaner M, Keaser ML, Krauthamer GM, Mantegna J, Dumas JA, Newhouse PA, Filippi CG, Keefe JF, Naylor MR. Cognitive-behavioral therapy increases prefrontal cortex gray matter in patients with chronic pain. J Pain. 2013;14(12):1573-84.
113. Schwedt TJ, Chong CD, Chiang CC, Baxter L, Schlaggar BL, Dodick DW. Enhanced pain-induced activity of pain-processing regions in a case-control study of episodic migraine. Cephalalgia. 2014;34(12):947-58.
114. Hubbard CS, Khan SA, Keaser ML, Mathur VA, Goyal M, Seminowicz DA. Altered Brain Structure and Function Correlate with Disease Severity and Pain Catastrophizing in Migraine Patients. eNeuro. 2014;1(1):e20.14.
115. Mathur VA, Khan SA, Keaser ML, Hubbard CS, Goyal M, Seminowicz DA. Altered cognition-related brain activity and interactions with acute pain in migraine. Neuroimage Clin. 2015;7:347-58.
116. Disner SG, Beevers CG, Haigh EA, Beck AT. Neural mechanisms of the cognitive model of depression. Nat Rev Neurosci. 2011;12(8):467-77.
117. Beaty RE, Kaufman SB, Benedek M, Jung RE, Kenett YN, Jauk E, Neubauer AC, Silvia PJ. Personality and complex brain networks: The role of openness to experience in default network efficiency. Hum Brain Mapp. 2016;37(2):773-9.
118. Mulders PC, van Eijndhoven PF, Schene AH, Beckmann CF, Tendolkar I. Resting-state functional connectivity in major depressive disorder: A review. Neurosci Biobehav Rev. 2015;56:330-44.

119. Kucyi A, Davis KD. The dynamic pain connectome. Trends Neurosci. 2015;38(2):86-95.
120. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007;370(9590):851-8.
121. Lipton RB, Munjal S, Buse DC, Fanning KM, Bennett A, Reed ML. Predicting Inadequate Response to Acute Migraine Medication: Results From the American Migraine Prevalence and Prevention (AMPP) Study. Headache. 2016;56(10):1635-48.
122. Yu R, Gollub RL, Vangel M, Kaptchuk T, Smoller JW, Kong J. Placebo analgesia and reward processing: Integrating genetics, personality, and intrinsic brain activity. Hum Brain Mapp. 2014;35(9):4583-93.
123. Quilty LC, De Fruyt F, Rolland JP, Kennedy SH, Rouillon PF, Bagby RM. Dimensional personality traits and treatment outcome in patients with major depressive disorder. J Affect Disord. 2008;108(3):241-50.
124. Rapinesi C, Del Casale A, Scatena P, Kotzalidis GD, Di Pietro S, Ferri VR, Bersani FS, Brugnoli R, Raccah NR, Zangen A, Ferracuti S, Orzi F, Girardi P, Sette G. Add-on deep Transcranial Magnetic Stimulation (dTMS) for the treatment of chronic migraine: A preliminary study. Neurosci Lett. 2016;623(3):7-12.
125. Cousins G, Hijazze S, Van de Laar FA, Fahey T. Diagnostic accuracy of the ID Migraine: a systematic review and meta-analysis. Headache. 2011;51(7):1140-8.
126. Smitherman TA, Burch R, Sheikh H, Loder E. The prevalence, impact, and treatment of migraine and severe headaches in the United States: a review of statistics from national surveillance studies. Headache. 2013;53(3):427-36.
127. Lombard L, Farrar M, Ye W, Kim Y, Cotton S, Buchanan AS, Jackson J, Joshi S. A global real-world assessment of the impact on health-related quality of life and work productivity of migraine in patients with insufficient versus good response to triptan medication. J Headache Pain. 2020;21(41):1-16.
128. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. Transformed migraine and medication overuse in a tertiary headache centre--clinical characteristics and treatment outcomes. Cephalalgia. 2004;24(6):483-90.

129. Gallagher RM, Kunkel R. Migraine medication attributes important for patient compliance: concerns about side effects may delay treatment. Headache. 2003;43(1):36-43.

130. Yang. CP, Liang. CS, Chang. CM, Yang. CC, Shih. PH, Yau. YC, Tang K-T, Wang S-J. Comparison of New Pharmacologic Agents With Triptans for Treatment of Migraine: A Systematic Review and Meta-analysis. JAMA Netw Open. 2021;4(10):e2128544.

131. Negro. A, Martelletti. P. Gepants for the treatment of migraine. Expert Opin Investig Drugs. 2019;28(6):555-67.

132. Stewart W, Breslau N, Keck PE. Comorbidity of migraine and panic disorder. Neurology. 1994;44(10):23-7.

133. Jette N, Patten S, Williams J, Becker W, Wiebe S. Comorbidity of Migraine and Psychiatric Disorders--A National Population-Based Study. Headache. 2008;48(4):501-16.

134. Gámiz MJ, Lopez-Escamez JA. Health-related quality of life in patients over sixty years old with benign paroxysmal positional vertigo. Gerontology. 2004;50(2):82-6.

135. Anderson JP, Harris JP. Impact of Ménière's disease on quality of life. Otol Neurotol. 2001;22(6):888-94.

136. Rammohan K, Mundayadan SM, Das S, Shaji CV. Migraine and Mood Disorders: Prevalence, Clinical Correlations and Disability. J Neurosci Rural Pract. 2019;10(1):28-33.

137. Chu HT, Liang CS, Lee JT, Yeh TC, Lee MS, Sung YF, Yang F-C. Associations Between Depression/Anxiety and Headache Frequency in Migraineurs: A Cross-Sectional Study. Headache. 2018;58(3):407-15.

138. Ligthart L, Hottenga JJ, Lewis CM, Farmer AE, Craig IW, Breen G, Willemsen G, Vink JM, Middledorp CM, Byrne EM, Heath AC, Madden PAF, Pergadia ML, Montgomery GW, Martin NG, Penninx BWJH, McGuffin P, Boomsma DI, Nyholt DR. Genetic risk score analysis indicates migraine with and without comorbid depression are genetically different disorders. Hum Genet. 2014;133(2):173-86.

139. Schwedt T, Hentz J, Sahai-Srivastava S, Spare N, Martin V, Treppendahl C, Digre K, Bennett NL, Birlea M, Watson D, Murinova N, Robert T, Dodick DW, MOTS Investigators. Headache characteristics and burden from chronic migraine with

medication overuse headache: Cross-sectional observations from the Medication Overuse Treatment Strategy trial. Headache. 2021;61(2):351-62.

140. Doane M, Gupta S, Vo P, Laflamme A, Fang J. Associations Between Headache-Free Days and Patient-Reported Outcomes Among Migraine Patients: A Cross-Sectional Analysis of Survey Data in Europe. Pain Ther. 2019;8(2):203-16.

141. Kim S, Park S. The role of headache chronicity among predictors contributing to quality of life in patients with migraine: a hospital-based study. J Headache Pain. 2014;15(1):68.

142. Vo P, Fang J, Bilitou A, Laflamme A, Gupta S. Patients' perspective on the burden of migraine in Europe: a cross-sectional analysis of survey data in France, Germany, Italy, Spain, and the United Kingdom. J Headache Pain. 2018;19(1):82.

143. Bordini. CA, Mariano da Silva. H, Garbelini. RP, Teixeira. SO, Speciali. JG. Effect of preventive treatment on health-related quality of life in episodic migraine. J Headache Pain. 2005;6(5):387-91.

144. Dodick. DW, Silberstein. S, Saper. J, Freitag. FG, Cady. RK, Rapoport. AM, Mathew NT, Hulihan J, Crivera C, Rupnow MFT, Mao L, Finlayson G, Greenberg SJ. The impact of topiramate on health-related quality of life indicators in chronic migraine. Headache. 2007;47(10):1398-408.

145. D'Amico. D, Solari. A, Usai. S, Santoro. P, Bernardoni. P, Frediani. F, Marco RD, Massetto N, Bussone G, Progetto Cefalee Lombardia Group. Improvement in quality of life and activity limitations in migraine patients after prophylaxis. A prospective longitudinal multicentre study. Cephalalgia. 2006;26(6):691-6.

146. Spierings. ELH, Ning. X, Ramirez Campos. V, Cohen. JM, Barash. S, Buse. DC. Improvements in quality of life and work productivity with up to 6 months of fremanezumab treatment in patients with episodic and chronic migraine and documented inadequate response to 2 to 4 classes of migraine-preventive medications in the phase 3b FOCUS study. Headache. 2021;61(9):1376-86.

147. Cainazzo. MM, Baraldi. C, Ferrari. A, Lo Castro. F, Pani. L, Guerzoni. S. Erenumab for the preventive treatment of chronic migraine complicated with medication overuse headache: an observational, retrospective, 12-month real-life study. Neurol Sci. 2021;42(10):4193-202.

148. Negro. A, Curto. M, Lionetto. L, Crialesi. D, Martelletti. P. OnabotulinumtoxinA 155 U in medication overuse headache: a two years prospective study. SpringerPlus. 2015;4:826.
149. Paemeleire K, Bahra A, Evers S, Matharu MS, Goadsby PJ. Medication-overuse headache in patients with cluster headache. Neurology. 2006;67(1):109-13.
150. Finch JF, Baranik LE, Liu Y, West SG. Physical health, positive and negative affect, and personality: A longitudinal analysis. J Res Pers. 2012;46(5):537-45.
151. Costa PT, McCrae RR. Influence of extraversion and neuroticism on subjective well-being: happy and unhappy people. J Pers and social psychology. 1980;38(4):668-78.
152. Chapman B, Duberstein P, Lyness JM. Personality traits, education, and health-related quality of life among older adult primary care patients. J Gerontol B Psychol Sci Soc Sci. 2007;62(6):343-52.
153. Pocnet C, Dupuis M, Congard A, Jopp D. Personality and its links to quality of life: Mediating effects of emotion regulation and self-efficacy beliefs. Motiv Emot. 2017;41(2):196-208.
154. Andrasik F. What does the evidence show? Efficacy of behavioural treatments for recurrent headaches in adults. Neurol Sci. 2007;28:70-7.
155. Antonaci F, Dumitrache C, De Cillis I, Allena M. A review of current European treatment guidelines for migraine. J Headache Pain. 2010;11(1):13-9.
156. Bendtsen L, Evers S, Linde M, Mitsikostas D, Sandrini G, Schoenen J. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. Eur J Neurol. 2010;17(11):1318-25.

9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Publications related to the thesis

Magyar M, Gonda X, Pap D, Edes A, Galambos A, Baksa D, Kocsel N, Szabo E, Bagdy G, Elliott R, Kokonyei G, Juhasz G. Decreased Openness to Experience Is Associated with Migraine-Type Headaches in Subjects with Lifetime Depression. Front Neurol. 2017 22;(8):270. doi: 10.3389/fneur.2017.00270.

Magyar M, Kökönyei Gy, Baksa D, Galambos A, Édes A E, Szabó E, Kocsel N, Gecse K, Dobos D, Gyüre T, Juhász G, Ertsey Cs. A cross-sectional study on the quality of life in migraine and medication overuse headache in a Hungarian sample: understanding the effect of headache characteristics. Ideggyogy Sz. 2022;75(7-8):253-63.

9.2. Other publications

Baksa D, Szabo E, Kocsel N, Galambos A, Edes AE, Pap D, Zsombok T, **Magyar M**, Gecse K, Dobos D, Kozak LR, Bagdy G, Kokonyei G, Juhasz G. Circadian Variation of Migraine Attack Onset Affects fMRI Brain Response to Fearful Faces. Front Hum Neurosci. 2022;9;(16):842426. doi: 10.3389/fnhum.

Magyar M, Glasz T, Kovács T, Deák A B., Maurovich-Horvat P., Futácsi B. Liver displacement caused by distended stomach in Parkinsonian patient. Imaging. 2021;13(1):76-79. doi: 10.1556/1647.2021.00004

Magyar M, Nyilas NL, Bereczki D, Bozsik G, Rudas G, Ertsey C, Maurovich-Horvat P, Barsi P. A spontán intracranialis hypotensio diagnosztikája mágneses rezonanciás képalkotással [Evaluation and diagnosis of spontaneous intracranial hypotension with magnetic resonance imaging]. Orv Hetil. 2021;162(7):246-51. Hungarian. doi: 10.1556/650.2021.31961.

Magyar M, Barsi P, Korányi K, Kaposi P. Thrombosed orbital varix with mild, spontaneously resolving symptoms. Imaging. 2020.;12(1), 1-3. doi: 10.1556/1647.2020.00001

Dióssy M, Balogh E, **Magyar M**, Gyüre T, Csépány É, Bozsik G, Ertsey C. Az életminőség vizsgálata a cluster fejfájás aktív időszakában [The quality of life of the cluster headache patients during the active phase of the headache]. Ideggyogy Sz. 2020;73(1-2):15-26. Hungarian. doi: 10.18071/isz.73.0015.

Edes AE, McKie S, Szabo E, Kokonyei G, Pap D, Zsombok T, **Magyar M**, Csepany E, Hullam G, Szabo AG, Kozak LR, Bagdy G, Juhasz G. Increased activation of the pregenual anterior cingulate cortex to citalopram challenge in migraine: an fMRI study. BMC Neurol. 2019;19(1):237. doi: 10.1186/s12883-019-1478-0.

Kocsel N, Galambos A, Szabó E, Édes AE, **Magyar M**, Zsombók T, Pap D, Kozák LR, Bagdy G, Kökönyei G, Juhász G. Altered neural activity to monetary reward/loss processing in episodic migraine. Sci Rep. 2019;9(1):5420. doi: 10.1038/s41598-019-41867-x.

Ertsey C, **Magyar M**, Gyüre T, Balogh E, Bozsik G. A tenziós fejfájás és kezelése [Tension type headache and its treatment possibilities]. Ideggyogy Sz. 2019;72(1-2):13-21. Hungarian. doi: 10.18071/isz.72.0013.

Csépány É, Tóth M, Gyüre T, **Magyar M**, Bozsik G, Bereczki D, Juhász G, Ertsey C. The validation of the Hungarian version of the ID-migraine questionnaire. J Headache Pain. 2018;19(1):106. doi: 10.1186/s10194-018-0938-z.

Edes AE, Kozak LR, **Magyar M**, Zsombok T, Kokonyei G, Bagdy G, Juhasz G. Spontaneous migraine attack causes alterations in default mode network

connectivity: a resting-state fMRI case report. BMC Res Notes. 2017;10(1):165. doi: 10.1186/s13104-017-2484-1.

Magyar M, Ertsey Cs, Bozsik Gy, Dióssy M, Csépány É, Gyüre T. Fejfájás a klinikai gyakorlatban. Háziorvosi Továbbképző szemle. 2017;22(9) 593-97.

Ertsey Cs, **Magyar M**, Csépány É, Gyüre T. Fejfájás és migrén gyógyszeres kezelési lehetőségei. Háziorvosi továbbképző szemle. 2017;21(1) 2-7.

Juhasz G, Csepany E, **Magyar M**, Edes AE, Eszlari N, Hullam G, Antal P, Kokonyei G, Anderson IM, Deakin JF, Bagdy G. Variants in the CNR1 gene predispose to headache with nausea in the presence of life stress. Genes Brain Behav. 2017;16(3):384-393. doi: 10.1111/gbb.12352.

Kokonyei G, Szabo E, Kocsel N, Edes A, Eszlari N, Pap D, **Magyar M**, Kovacs D, Zsombok T, Elliott R, Anderson IM, William Deakin JF, Bagdy G, Juhasz G. Rumination in migraine: Mediating effects of brooding and reflection between migraine and psychological distress. Psychol Health. 2016;31(12):1481-1497. doi: 10.1080/08870446.2016.1235166.

Magyar M, Csépány É, Gyüre T, Bozsik G, Bereczki D, Ertsey C. A triciklusos antidepresszívumok helye a fejfájások kezelésében [Tricyclic antidepressant therapy in headache]. Neuropsychopharmacol Hung. 2015;17(4):177-82. Hungarian. PMID: 26727721.

Csépány É, **Magyar M**, Gyüre T, Bozsik G, Ertsey C. A migrén korszerű farmakoterápiája [Current pharmacotherapy in migraine]. Neuropsychopharmacol Hung. 2015;17(4):169-76. Hungarian. PMID: 26727720.

Magyar M, Hajnal B, Gyüre T, Ertsey C. Fájdalomcsillapító-túlhasználathoz társuló fejfájás [Medication-overuse headache]. Orv Hetil. 2015;156(30):1195-202. Hungarian. doi: 10.1556/650.2015.30209.

10. **ACKNOWLEDGEMENTS**

I would like to express my gratitude to my supervisors Associate Professor Dr. Gabriella Juhász and Associate Professor Dr. Csaba Ertsey for introducing me into the interesting fields of headache and quality of life research, for their continuous, patient and kind support and guidance throughout all my PhD years, in all my posters, presentations, papers and all of my work in the research group.

Similarly, I am really grateful to the Head of the Department of Neurology at Semmelweis University, Professor Dr. Dániel Bereczki for providing opportunity to work at the Headache Department and for his guidance and advices in my work and career.

Moreover, I also thank the support to all my other colleagues and co-authors, for the great papers I was involved in at the Department of Neurology: Dr. Terézia Zsombók, Dr. György Bozsik, Dr. Éva Csépány and Tamás Gyüre and at the Department of Pharmacodynamics: Dr. Gyöngyi Kökönyei, Dr. Edina Szabó, Dr. Natália Kocsel, Dr. Kinga Gecse, Dr. Andrea Édes, Dóra Dobos, Dániel Baksa, Attila Galambos, Dr. Nóra Eszlári.

I would like to express my gratitude to our participants. These projects could not have been completed without their contribution.

The greatest “Thank you!” is going to my Family (Anya, Apa, my brother Donát) and my wife Rita for their continuous love and support.

Finally, last but not least, I would list the financial support: the studies included to this thesis were supported by the Hungarian Brain Research Program (Grants: 2017-1.2.1-NKP-2017-00002 - SE NAP2 Genetic Brain Imaging Migraine Research Group; KTIA_NAP_13-2- 2015-0001 - MTA-SE-NAP B Genetic Brain Imaging Migraine Research Group); by the Hungarian Academy of Sciences (MTA-SE Neuropsychopharmacology and Neurochemistry Research Group); and by the Thematic Excellence Programme (Tématerületi Kiválósági Program, 2020-4.1.1.-TKP2020) of the Ministry for Innovation and Technology in Hungary, within the framework of the Neurology and Translational Biotechnology thematic programmes of the Semmelweis University.