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PAINMIG: studio di coorte per la valutazione del dolore mentale in pazienti affetti da emicrania

PAINMIG: Cohort Study for the Evaluation of Mental Pain in Migraine Patients

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Abstract

Background: Migraine is a disabling primary headache disorder that may interfere with patients' psychological status, quality of life, and functioning. Over the past decades, the psychosomatic research has advanced in dealing with complex biopsychosocial phenomena and it has provided new effective modalities of assessment. In this framework, mental pain was highlighted as a unitary subjective state of psychological and emotional suffering resulting from the experience of loss, sense of emptiness and feeling broken accompanied by strong negative feelings such as guilt, fear, anxiety, loneliness, helplessness, loss of self, and disconnection. Nevertheless, migraine evaluation according to psychosomatic principles, including mental pain and biopsychosocial variables that might affect its course has been poorly performed. The present study was aimed at evaluating psychosomatic, psychosocial, and psychological variables as potential risk and protective factors for migraine. Moreover, it aims to investigate psychosomatic, psychosocial, and psychiatric variables patients as potential risk and protective factors for mental pain in migraine subjects.

Methods: A cohort study design was applied. Two-hundred subjects were enrolled at the Headache Center of the Careggi University Hospital (Florence, Italy): 100 subjects had a diagnosis of chronic migraine (CM) and 100 had a diagnosis of episodic migraine (EM). One-hundred healthy subjects (HS) were also enrolled from the general population of Central Italy as healthy controls (ratio case: control = 2:1). Participants completed a clinical assessment including: ID Migraine; Migraine Disability Assessment Questionnaire (MIDAS); Brief Pain Inventory (BPI); the Structured Clinical Interview for DSM-5 (SCID-5); Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview (DCPR-R-SSI); Clinical Interview for Depression (CID); PsychoSocial Index (PSI); Mental Pain Questionnaire (MPQ); Euthymia Scale (ES).

Results: Among the variables taken into account higher levels of CID anxiety (OR = 1.39; 95% CI = 1.07–1.72; p = 0.012) and PSI psychological distress (OR = 1.24; 95% CI = 1.06–1.45; p = 0.007) were found as risk factors for EM as compared to HS, whereas PSI quality of life (OR = 0.50; 95% CI = 0.29–0.88; p = 0.016) was found as protective factor for EM as compared to HS. Mental pain (OR = 1.20; 95% CI = 1.01–1.50; p = 0.007) and PSI psychological distress (OR = 1.22; 95% CI = 1.07–1.36; p = 0.002) were

found as risk factors for CM as compared to HS, whereas ES well-being (OR = 0.70; 95% CI = 0.55–0.90; p = 0.006) was found as protective factor for CM as compared to HS. Higher mental pain (OR = 1.31; 95% CI = 1.08–1.59; p < 0.001) and PSI psychological distress (OR = 1.08; 95% CI = 1.00–1.16; p = 0.045) were found as risk factors for EM as compared to CM, whereas ES psychological well-being (OR = 0.73; 95% CI = 0.55–0.96; p = 0.027) was found as significant protective factor for EM as compared to CM. CID depression (OR = 1.06; 95% CI = 1.00–1.13; p = 0.046) and PSI psychological distress (OR = 1.20; 95% CI = 1.01–1.50; p = 0.007) were found risk factors for having mental pain in migraine subjects, whereas ES psychological well-being (OR = 0.69; 95% CI = 0.53–0.95; p = 0.007) and PSI psychosocial well-being (OR = 0.44; 95% CI = 0.31–0.70; p = 0.001) were found as protective factors for having mental pain in migraine subjects.

Conclusion: The assessment of migraine subjects which aims at being comprehensive according to psychosomatic principles should include the Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R), the Mental Pain Questionnaire (MPQ), and the Euthymia Scale (ES). Mental pain is a psychosomatic variable deserving attention in chronic migraine patients. ES well-being is a protective factor for both chronic migraine and mental pain.

Keywords: Migraine, Mental Pain, Psychosomatic Medicine, Diagnostic Criteria for Psychosomatic Research-Revised, Euthymia.

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1 The Psychosomatic Medicine

1.1 Historical Background

Psychosomatic medicine is a comprehensive and interdisciplinary framework that represents an alternative model to biomedically oriented medicine (e.g., Fava & Sonino, 2007; Fava, Sonino, & Wise, 2010; Fava, Cosci, & Sonino, 2017). Biomedicine is mainly focused on what is treatable with drugs and conceptualizes behavioural phenomena of disease in terms of physicochemical principles (Fava & Sonino, 2007). On the contrary, psychosomatic medicine is a scientific approach that has integrated a biopsychosocial and a psychological view of the patients' care providing an innovative framework for clinics and research (Fava, Cosci, & Sonino, 2017).

Psychosomatic medicine originated from the complex interactions between medicine, psychiatry, psychology, and philosophy (Grassi, Wise, Cockburn, Caruso, & Riba, 2019). The first references to the term "psycho-somatic" were provided in 1818 by Johan Christian August Heinroth (1773-1843) (Heinroth, 1818). He was the first holder of a chair of psychiatry in Europe at Leipzig University and provided the first attempt to formulate a system of psychotherapy (Harms, 1959; Marx, 2008a). Heinroth introduced the term psycho-somatic (i.e., psychisch-somatisch) to describe the origin of insomnia in a rather cryptic sentence: "As a general rule, the origin of insomnia is psycho-somatic, but it is possible that every phase of life can itself provide the complete reason for insomnia" (Translation by Margretts, 1950) (p. 403). ["Gewöhnlich sind die Quellen der Schlaflosigkeit psychisch-somatisch, doch kann auch jede Lebenssphäre für sich allein den vollständigen Grund derselben enthalten." (Heinroth, 1818) (p. 49, vol. 2)]. Stainberg and Wallace illustrated the meaning of the word psychosomatic used by Heinroth considering his compendium of psychopathology (Stainberg, 2007; Wallace, 2008). Heinroth differentiated mental disorders in two categories: disturbances associated with physical illness (i.e., psychological symptoms caused by an organic disorder) and actual mental disturbances (i.e., psychological symptoms without an observable anatomical pathology) (Stainberg, 2007). In the etiology of the actual mental disturbances, Heinroth stated that the soul (i.e., psychological aspects) has the primacy over the body (Stainberg, 2007). Starting for this premise, Stainberg and Wallace purposed that Heinroth used the word psycho-somatic to describe a symptom (i.e., insomnia) in which the etiology is more frequently psychological (Stainberg, 2007; Wallace, 2008).

The second early author that applied the term psychosomatic was the German psychiatrist and philosopher Friedrich Groos (1768-1852), director of the combined hospice and madhouse in Pforzheim (Margrestts, 1950; Marx, 2008a). Groos used the term psychosomatic to describe his theory on the etiology of mental disorder (Groos, 1828). Groos considered that a healthy mind constantly tries to realize good things for the patient (Groos, 1828). On the contrary, a weakening or absence of this mental function constituted the basis of mental disorder (Groos, 1828). Groos named this absence, the "psychic negative". In addition, Groos considered another factor that could be involved in the occurrence of a mental disorder that he called "somatic positive" (Groos, 1828). The somatic positive consists of an anatomical illness or a malfunctioning in the central nervous system (Groos, 1828). Thus, according to Groos the insurgence of a mental disorder required the presence of a psychic negative plus the presence of a somatic positive (Groos, 1828). In this framework, Gross used the term psychosomatic to describe the fact that both psychological and somatic factors played a role in the insurgence of a mental disorder (Margretts, 1950). Thus, the meaning of the word psychosomatic according to Gross was that a mental disorder originated from the interaction of physical and psychological factors (Margretts, 1950).

The American psychiatrist Clarence Bynold Farrar (1874-1970) translated for the first time the German term psychisch-somatisch into the English term psycho-somatic (Margretts, 1950). Despite this, during the early twentieth century, this adjective surfaced infrequently in English medical literature and the subject matter of psychosomatic medicine became more defined in the first third of the twentieth century (Weiner, 2008) when the World War II broke out (i.e., in 1939), thus accelerating the escape from the Nazi regime to the United States of several psychoanalysts (Lipsitt, 2001). They brought with them a new notion of mental illness and, as Weiner well summarized, early psychosomatic medicine in the United States originated from the convergence of American and European ideas (Weiner, 2008).

In Europe, during the first two decades of the twentieth century, psychoanalysts introduced a new meaning of the term psychosomatic different from that used by the early German psychiatrists (Weiner, 2008). According to psychoanalytic theories, the term psychosomatic referred mainly to the complex role of psychological factors in the etiology of a medical disease (Callan, 1979; Lipsitt, 2001). This approach stressed that psychic forces, conflicts, and unconscious factors were the cause of vulnerability to certain physical symptoms (Grassi et al., 2019). Thus, following this principle, the Viennese psychiatrist and psychoanalyst Felix Deutsch (1858-1928) introduced the term "psychosomatic medicine" in 1922 to describe the study of psychological factors involved in physical symptoms in the medical ill (Lipsitt, 2001). In this perspective, psychosomatic medicine aimed to ascertain how mental phenom-

ena could influence the body to foster vulnerabilities for causing medical disorders (Callan, 1979; Lipsitt, 2001). When, during the 1930s and 1940s, the major figures in psychosomatic escaped from Europe to the United States, i.e., Franz Gabriel Alexander, George Groddeck, Michael Balint, Ernst Simmel, Felix Deutsch, Eduardo Weiss, and later Angel Garma and Melitta Sperling, psychosomatic medicine began to be known and accepted in American academic institutions (Weiner, 2008). In this new context, the work of Franz Gabriel Alexander (1891-1969), psychoanalyst and physician, aroused a great deal of interest (Lipowski, 1986; Weiner, 2008; Jacob & Dunbar-Jacob, 2015). He studied the psychosomatic factors in seven specific illnesses: peptic duodenal ulcer, asthma, rheumatoid arthritis, neurodermatitis, essential hypertension, hyperthyroidism, and chronic inflammatory bowel disease (Alexander, 1950). He theorized that unconscious conflicts aroused chronic emotional tensions, whose physiological correlates might result in dysfunction of and, consequently, structural changes in specific target organs (Alexander, 1950).

In opposition to the theory of Alexander, Helen Flanders Dunbar (1909-1952) promoted a different approach to psychosomatic medicine in which negative emotions and stressors foster the vulnerabilities for causing medical illnesses (Dunbar, 1935). In her book "Emotions and Bodily Changes", Dunbar used the term psychosomatic medicine to describe a new holistic approach to medical practice (Dunbar, 1935). More particularly, Dunbar was a follower of the Swiss psychiatrist Adolf Meyer (1866-1950) and she introduced Meyer's psychobiological theory in early psychosomatics background (Lipowski, 1986; Powell, 1977). The psychobiological theory considers the emergence of a mental disorder as influenced by the interaction between the patient's unhealthy reactions to their environment and their biological susceptibility (Pilgrim, 2002). According to this principle, unhealthy reactions to the environment such as chronic stress or negative emotions may influence physiological processes (Dunbar, 1935). Dunbar based her studies on the evidence of the psychophysiological investigations on the stress of Walter Bradford Cannon (1871-1945) and Hans Selye (1907-1982) (Cannon, 1915; Selye, 1956). Cannon investigated the physiologic activation associated with the fight-flight reaction and the role of homeostasis in physiology (Cannon, 1915). Selye systematically studied stress that led to the elucidation of the general adaptation syndrome through the activation of the hypothalamic-pituitary-adrenal (HPA) axis (Selye, 1956).

The above theories were further illustrated in association with the psychobiological theory in the book "Stress and Disease" by Harold G. Wolff (Wolff, 1952). He purposed that psychological stress and stressful life changes as contributory causal factors in human diseases (Wolff, 1952). For example, Wolff hypothesized that disruption of family or social structures, deprivation of basic human needs, and the obstacles to the fulfillment of personal objectives were examples of stressful events

with pathogenic potential (Wolff, 1952). Moreover, a variety of stressful stimuli such as the death of a loved person, marriage, retirement, loss of a job, and the outbreak of war could be potentially noxious (Wolff, 1952).
Dunbar's and Wolff's books aroused the interests of the American society (Margretts, 1950; Lipowski, 1985; 1986). Dunbar, together with a group of researchers of the Columbia University, was the founder of the American Psychosomatic Society and its journal Psychosomatic Medicine that promoted the knowledge of psychosomatic medicine in the United States (Lipowski, 1985).

1.2 The Biopsychosocial Model

The studies of Alexander, Dunbar, Wolff, and Meyer exerted a great interest in view of their novelty and explanatory power, particularly in a field then dominated by psychoanalytic investigators (Fava & Sonino, 2000). However, these great expectations did not survive the test of scientific evidence (Fava & Sonino, 2000); progressively the internists left the field and a deep crisis strongly affected the psychosomatic medicine in the late fifties (Fava & Sonino, 2000).
In the sixties, Engel, Lipowski, and Kissen deserved credit for setting the ground for the renaissance of psychosomatic medicine under more appropriate guidelines (Fava & Sonino, 2000).

George Libman Engel (1913-1999) was trained in internal medicine at the Johns Hopkins University medical school, with a special interest in gastrointestinal disease: ulcerative colitis, the effect of psychogenic pain, and the effect of psychological states on gastric secretion in children with gastric fistula (Ghaemi, 2010). In the 1940s, Engel met the psychiatrist John Romano (1908-1994) during his training; he would follow Romano throughout his career, when Romano became chairman of psychiatry at the University of Cincinnati, and later at the University of Rochester where Engel spent the greater part of his life (Ghaemi, 2010). Encouraged by Romano, Engel took an interest in psychological aspects of gastrointestinal illness and engaged in formal training at the Institute for Psychoanalysis in Chicago, run by Franz Alexander (Ghaemi, 2010). In his clinical work at the University of Rochester, Engel mainly focused on understanding the psychological aspects of medical conditions (Fava, 2000), and his activities were characterized by the decreased attention to psychoanalytic models (Brown, 2003). Engel focused his activity on the education of medical students (Choen, 2000) introducing them to what he called the biopsychosocial model (e.g., Engel, 1960a; 1961b; 1977). This model was described by Engel in the paper "The need for a new medical model: A challenge for biomedicine" published in Science in 1977. The model recognized that illness and ill-health are influenced by the patient's biological, psychological, and

social variables, and that health is better understood as an integrated combination of these components (Engel, 1977). This was compared by Engel with the biomedical model of illness and ill-health which describes patients in terms of disease and excludes the psychological and social aspects of a person (Feinstein, 1987; Guillemin & Barnard, 2015). The seven point that Engel stressed in his critique to biomedicine are reported in table 1.

Table 1. Engel's critique of biomedicine. Adapted from Carrió-Suchman and Epstein (2004)

Point	Content
1	a. Biochemical alterations do not translate directly into an illness; b. the appearance of illness results from the interaction of diverse causal factors, i.e., molecular, individual, and social levels; c. psychological alterations may, under certain circumstances, manifest as illness.
2	The presence of a biological derangement does not shed light on the meaning that patient attributes to his symptoms.
3	Psychosocial variables are important determinants of susceptibility, severity, and course of illness; they should be considered together to biomedical variables.
4	To adopt a sick role is not necessarily associated with the presence of a biological derangement.
5	The success of the most biological of treatments is influenced by psychosocial factors, for example, the placebo effect.
6	The patient-clinician relationship influences medical outcomes, even if only because of its influence on adherence to a chosen treatment.
7	Patients are profoundly influenced by the way in which they are studied, and the scientists engaged in the study are influenced by their subjects.

In contrast to biomedicine, Engel proposed the biopsychosocial model as a new scientific and inclusive framework that could be applied to better understand the complex balance between health and disease (Engel, 1978). The Engel's biopsychosocial model adhered to the insights of general systems theory, developed by the biologists Ludwig von Bertalanffy and Paul Alfred Weiss (von Bertalanffy, 1977; Weiss, 1968). According to the general systems theory, the model applied a hierarchy of natural systems as its framework (Engel, 1977; 1980). In this context, the system included several levels of organization, beginning with the sub-atomic particle, to the single cell, through to the nervous system and the person (Engel, 1977; 1980). The lower half of the whole model represented the physical and biological

elements of the model (i.e., nervous system, organ, tissue, cell, organelle, and molecule) (Engel, 1977; 1980). The center of the model consisted of the person, which then extended through levels including the two-person (that is, the dyad), family, community, and ultimately to the biosphere (Engel, 1977; 1980). This upper-half represented the psychosocial or higher-order levels of organization in the natural hierarchy (Engel, 1982).

Each level can be examined and understood as a single element, in relation to its neighbors (and their neighbors) on the hierarchy, or in the context of the entire system (Engel, 1980). Figure 1 shows the hierarchy of natural systems and figure 2 illustrates the biopsychosocial model as a continuum.

Figure 1. The biopsychosocial model: Hierarchy of natural systems. Adapted from Engel (1980)

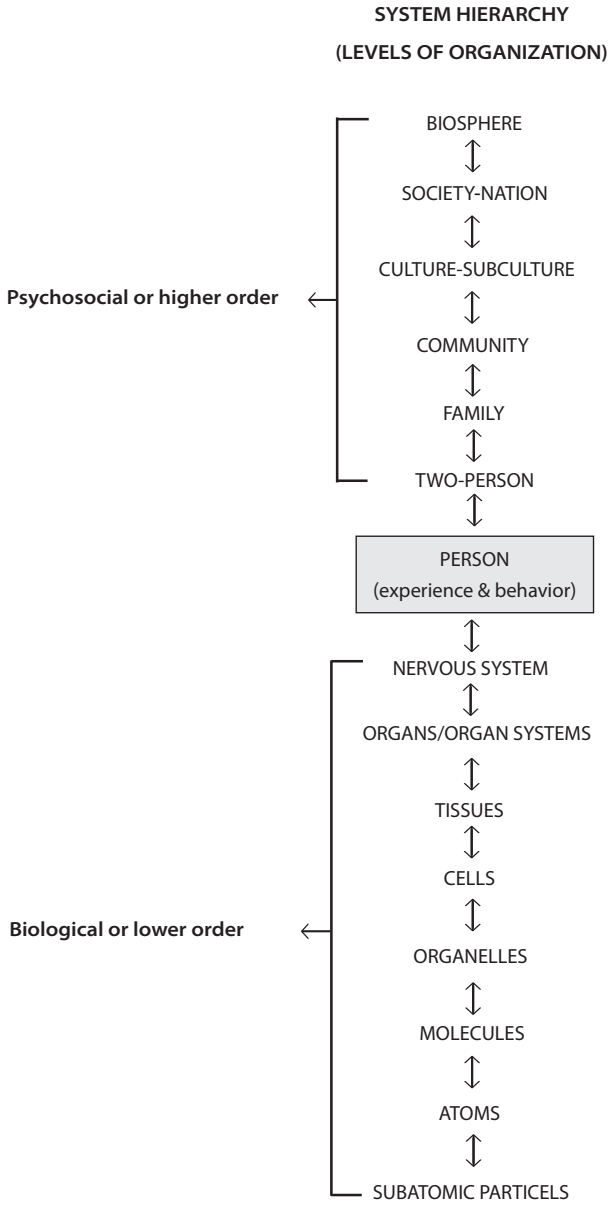
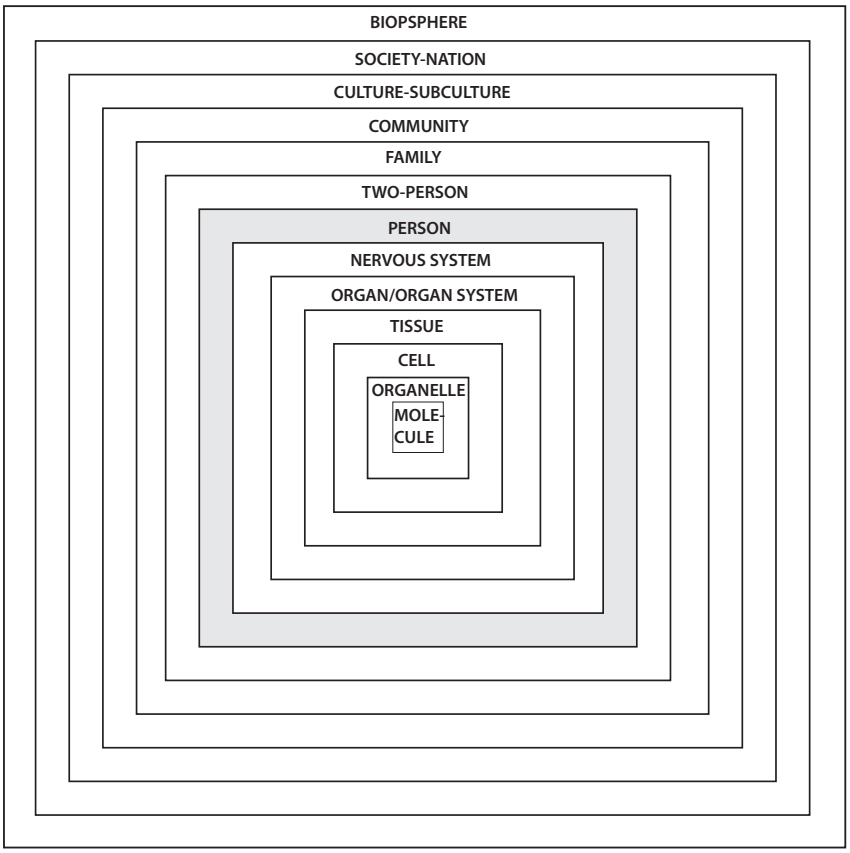


Figure 2. The biopsychosocial model as a continuum. Adapted from Engel (1980)



In 1980, Engel purposed the application of the biopsychosocial model to mental health in the paper entitled "The clinical application of the biopsychosocial model" published in the American Journal of Psychiatry (Engel, 1980). In this paper, he criticized the biomedically oriented psychiatry as a field limited to the study of sub-personal factors. In opposition, he purposed to conceptualize the balance between psychological health and disease as a phenomenon that emerges within the factors who are part of the whole biopsychosocial system (Engel, 1980). Hence, Engel described the attempts to study and treat mental disorders only referring to sub-personal factors as reductionist and highlighted two consequences of the reductionism: first, the diagnostic and etiological accounts derived from a biomedical approach would be partial and scientifically inadequate; second, such reductionist accounts might dehumanize the relationship between clinician and patient (Engel, 1980).

In summary, as Fava and Sonino remarked, the biopsychosocial model represents a multifactorial model of illness that "allows illness to be viewed as a result of interacting systems" at the cellular, tissue, organismic, interpersonal, and environmental levels in which "psychosocial factors may operate to facilitate, sustain or modify the course of disease, even though their relative weight may vary from illness to

illness, from one individual to another, and even between two different episodes of the same illness in the same individual" (Fava & Sonino, 2000) (p. 185).

Another contribution to the renaissance of psychosomatic medicine arose from the study of the Polish psychiatrist Zbigniew Jerzy Lipowski (1924-1997). Lipowski criticized the concept of psychosomatic disorder since it tended to perpetuate the obsolete notion of psychogenesis that was incompatible with the principle of multicausality, which constituted a core assumption of the biopsychosocial model (Lipowski, 1986). According to Fava and Sonino, Lipowski "gave an invaluable contribution in setting the scope, mission and methods of psychosomatic medicine" (Fava & Sonino, 2000) (p. 185). He identified three interrelated components that defined Psychosomatic Medicine: (1) it is a scientific discipline associated to the study of the relationships of biological, psychological, and social determinants of health and disease; (2) it includes a holistic approach to the practice of medicine; and (3) it encompasses consultation-liaison (CL) psychiatry (Lipowski, 1986).

In this framework, CL psychiatry refers to the practice and knowledge used to assess, treat, and prevent psychiatric morbidity in the medical ill in the form of psychiatric consultations, liaison, and teaching for non-psychiatric health workers, especially in the general hospital (Leigh, 2008; Fava, Sonino, & Wise, 2011). Even though Lipowski considered CL psychiatry as a part of Psychosomatic Medicine, Fava, Sonino, and Wise remarked that nowadays CL psychiatry is a separate field (Fava, Sonino, & Wise, 2011). They observed that CL psychiatry is clearly within only one field (i.e., psychiatry) and conversely Psychosomatic medicine is by definition multidisciplinary (Fava, Sonino, & Wise, 2011). In addition, Fava, Cosci, and Sonino noted that the developments of CL psychiatry are hindered by its modalities of assessment and treatment that followed a reductionist and psychiatric paradigm, thus missing the psychosocial background of its origin (Fava, Cosci, & Sonino, 2017). However, during the sixties and seventies, a formal training in CL psychiatry began in a number of general hospitals such as at the University of Rochester, at the Massachusetts General Hospital, at University of Cincinnati, at Montefiore Hospital–Albert Einstein Medical College in New York, and at Yale–New Haven Hospital (Leigh, 2008). Thus, the growth and development of CL psychiatry provided a strong clinical incentive to psychosomatic research and practice, but at the same time, it increased the psychiatric connotation of the field during these years (Fava & Sonino, 2000).

Table 2 shows the principle of psychosomatic medicine and CL psychiatry described by Lipowski in his book "Psychosomatic medicine and liaison psychiatry" published in 1985.

Table 2. Definition of psychosomatic medicine and liaison psychiatry. Adapted from Lipowski (1985)

Point	Content
1	Man is a biopsychosocial organism; one that receives, stores, processes, creates, and transmits information, and assigns meaning to it, which in turn elicits emotional responses.
2	Health and disease are determined by multiple factors: psychologic, social, and biologic factors, and always possess biopsychosocial aspects.
3	Study, prevention, diagnosis, and treatment of disease should take into account the varying contribution of all of the above three classes of variables.
4	Etiology is as a rule multifactorial. The relative weight of each class of causative factors, however, varies from disease to disease and from case to case; some are necessary and some only contributory.
5	Optimal patient care requires that the above postulates be applied in actual clinical practice.
6	Psychosocial factors must be considered in planning preventive and therapeutic measures.
7	The relationship between the patient and those taking care of him influences the course of illness and efficacy of treatment.
8	Psychotherapy may be of value whenever psychological factors are recognized as significantly contributing to the precipitation, maintenance, or exacerbation of any illness in a given person.

In the sixties, another pioneer in psychosomatic, David M. Kissen (1916-1968), the director and founder of the Psychosomatic Research Unit at the Southern General Hospital, Glasgow University (Bahnson, 1969), provided a further specification of the term psychosomatic (Fava & Sonino, 2000). He explained that the relative weight of psychosocial factors may vary significantly from one patient to another within the same illness and highlighted the basic conceptual flaw of considering diseases as homogeneous entities (Fava & Sonino, 2000). Moreover, Kissen was one of the first researcher in psychosomatics applying standardized questionnaires to investigate psychological aspects in medical patients (e.g., emotion and personality) such as the Maudsley Personality Inventory (MPI) (Bahnson, 1969; Kissen & Eysenck, 1962; Kissen, 1967).

Up to the seventies, psychosomatic medicine was the main site for research at the interface between medicine and behavioral sciences (Fava & Sonino, 2000).

However, in the same years two medical approaches were established: the behavioral medicine and the mind-body medicine (Fava & Sonino, 2000). These medical approaches shared same holistic and biopsychosocial connotation with psychosomatic medicine (Fava & Sonino, 2000). Thus, In the 21st century, a group of researchers provides a new definition of aims and methods of psychosomatic medicine to better differentiate it from behavioral medicine and mind-body medicine (i.e., Fava & Sonino, 2000; Fava, Cosci, & Sonino, 2017).

1.3 Current Psychosomatic Research and Practice

The first definition of modern psychosomatic medicine was provided by Fava and Sonino in 2000 and by Fava, Cosci, and Sonino who revised the aims and methods of psychosomatic medicine in 2017 (Fava & Sonino, 2000; Fava, Cosci, & Sonino, 2017). They defined psychosomatic medicine as a comprehensive and multidisciplinary field that "is concerned with the interaction of biological, psychological, and social factors in regulating the balance between health and disease" (Fava, Cosci, & Sonino, 2017) (p. 13). The authors provided four key points to describe the conceptual framework of psychosomatic medicine:

a. it encompasses scientific investigations on the role of psychosocial factors affecting individual vulnerability, course, and outcome of any type of medical illnesses;

b. it concerns the personalized and holistic approach to the patient adding the psychosocial assessment to the standard medical examination;

c. it provides the integration of psychological and psychiatric therapies in the prevention, treatment, and rehabilitation of medical illnesses;

d. it involves the multidisciplinary organization of health care (Fava, Cosci, & Sonino, 2017).

In this framework, the principle of psychosomatic assessment (i.e., assessment of psychosocial variables in the setting of medical disease) includes the clinimetric approach to the medical evaluation (Fava, Sonino, & Wise, 2012). The term "clinimetrics" was introduced in 1982 by Alvan R. Feinstein (1925-2001) (Feinstein, 1982). It indicates a domain concerned with indexes, rating scales, and other expressions that are used to describe or measure symptoms, physical signs, and other clinical phenomena that do not find room in customary clinical taxonomy (Feinstein, 1982; 1987). Such phenomena were labelled by Feinstein as "soft information" which comprises the psychosocial dimensions such as stress, lifestyle, well-being, illness behavior, and psychological symptoms (Feinstein, 1987; Fava, Tomba, & Sonino, 2011). Conversely, biomedical oriented psychiatry and clinical psychology em-

braced a reductionist and categorical approach based on psychometric tools such as the Diagnostic and Statistical Manual of mental disorders (DSM) (American Psychiatric Association, APA; 1987; 1994; 2013). More recently, a growing awareness has shown that also symptoms which do not reach the threshold of syndromes, as identified by the DSM diagnostic criteria, may affect the quality of life and entail pathophysiological and therapeutic implications (Fava, Tomba, & Sonino, 2011). This awareness led psychosomatic research to develop clinimetric instruments aimed at assessing Feinstein's "soft information" such as psychosocial functioning (i.e., the PsychoSocial Index) (Sonino & Fava, 1998; Piolanti et al., 2016), psychosocial syndromes (i.e., the Diagnostic Criteria for Psychosomatic Research) (Fava et al., 1995; Fava, Cosci, & Sonino, 2017), euthymia (i.e., the Euthymia Scale) (Fava & Bech, 2016; Carrozzino et al., 2019), and mental pain (i.e., the Mental Pain Questionnaire) (Fava, 2016; Svicher et al., 2019).

2 Psychosocial Syndromes: the Diagnostic Criteria for Psychosomatic Research

According to the clinimetric principles, an international group of investigators developed the Diagnostic Criteria for Psychosomatic Research (DCPR) in 1995 (Fava et al., 1995). The DCPR is a diagnostic system aimed to evaluate psychosocial syndromes (Fava et al., 1995) and recognize health-related problems affecting daily functioning and influencing symptom presentation (Porcelli & Sonino, 2007). In this perspective, medical illness is viewed as the common final pathway resulting from a dynamic balance between health and disease (Fava, Cosci, & Sonino, 2017). This balance is provided by the interaction of the biopsychosocial systems that may modulate the vulnerability or the course, prognosis, and rehabilitation of physical diseases (Porcelli & Sonino, 2007). DCPR approach includes a set of 12 diagnostic criteria for psychosocial syndromes (Fava et al., 1995). The 12 clusters are related with alexithymia, type A behavior, disease phobia, thanatophobia, health anxiety, illness denial, functional somatic symptoms secondary to psychiatric disorders, persistent somatization, conversion symptoms, anniversary reactions, irritable mood, and demoralization (Fava et al., 1995).

Another reason to develop the DCPR stemmed from the limited clinical utility that the Diagnostic and Statistical Manual of mental disorders nosography (APA, 1987; 1994; 2000) has sowed in psychosomatics (Cosci & Fava, 2016).

Cosci and Fava critically examined the DSM classification system highlighting that also the fifth edition (DSM-5; APA, 2013) did not give room to psychosocial clinical phenomena such as demoralization, allostatic overload, and hypochondriasis which do exist in the clinical realm (Cosci & Fava, 2016; 2019). Indeed, they indicated several limitations of the DSM-5 section of somatic symptoms disorder and other disorders that is the most specific section for the medically ill (Cosci & Fava, 2019). This category encompasses the diagnoses of somatic symptom disorder, illness anxiety disorder, conversion disorder, psychological factors affecting other medical conditions, factitious disorder, other specified somatic symptom and related disorder, and unspecified somatic symptom and related disorder (APA, 2013).

Somatic symptom disorder is defined by the presence of one or more distressing somatic symptoms (Criterion A), which may or may not be associated with another medical condition (APA, 2013; Bailer et al., 2015; Pannekoek & Stein, 2014). These symptoms are accompanied by maladaptive thoughts (i.e., disproportionate and persistent thoughts about the seriousness of one's symptoms), feelings (i.e., persistently high levels of anxiety about health or symptoms) or behaviors (i.e., ex-

cessive time and energy devoted to these symptoms or health concerns) (Criterion B) (APA, 2013). Fava and Cosci remarked that the presence of distressing somatic symptoms is not necessarily associated only with anxiety and concerns about health or symptoms (Cosci & Fava, 2019). On the contrary, these symptoms could lead to other clinical manifestations such as demoralization and irritability (Cosci & Fava, 2019). In addition, they remarked a lack of specificity of the DSM-5 criterion B, since it entails a wide variability in the clinician's judgment (Cosci & Fava, 2019). Thus, the diagnosis of somatic symptom disorder has poor specificity and de-emphasizes the role of the maladaptive affective responses to medically unexplained symptoms (Cosci & Fava, 2019).

On the opposite, the diagnosis of DSM-5 illness anxiety disorder is to be considered when there are extensive worries about health, maladaptive health-seeking or avoidant behavior but few or no somatic symptoms (APA, 2013). In turn, only patients presenting with high health anxiety but without somatic symptoms will receive the DSM-5 diagnosis of illness anxiety disorder (APA, 2013). However, Fava and Cosci highlighted that the definition does not include the hypervigilance to bodily symptoms showing a clear absence of insight specifiers as well as it is characterized by the presence of overlapping criteria with the diagnosis of somatic symptom disorder (Cosci & Fava, 2019). Moreover, DSM-5 discarded the dimensional features of health anxiety and advanced that illness-related preoccupation should not be better explained by another mental disorder (Cosci & Fava, 2019). Thus, according to Cosci and Fava the differential diagnosis is unclear since repetitive safety-seeking behaviors are common in other mental disorders (e.g., obsessive-compulsive disorder or body dysmorphic disorder) and illness phobia, health anxiety, or fear of disease are common prodromal symptoms of panic (Cosci & Fava, 2016; 2019).

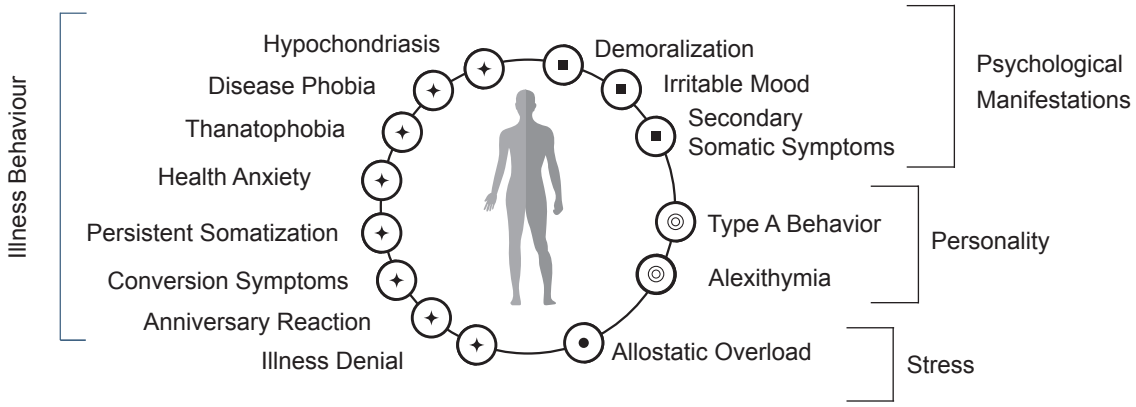
In the DSM-5 diagnosis of conversion, the DSM-IV criterion concerning the presence of psychological factors preceding the initiation or the exacerbation of symptoms (Criterion B) was removed (Cosci & Fava, 2019). Again, Cosci and Fava remarked a possible lack of sensitivity of the diagnosis of conversion since it depends on the accuracy of the medical examinations, even though 30% of outpatients who attend neurological facilities have symptoms not explained by medical findings (Cosci & Fava, 2019).

The DSM-5 removed the diagnosis of hypochondriasis (Cosci & Fava, 2019). Cosci and Fava deeply criticized this choice since it arbitrarily postulated that the majority of patients with DSM-IV hypochondriasis would meet the criteria for somatic symptom disorder and the remaining part would be subsumed under the diagnosis of illness anxiety disorder (Cosci & Fava, 2016). Moreover, they highlighted that the distinctive features of hypochondriasis, which include preoccupation, anxiety, bodily hypervigilance, and avoidance behaviors, were lost in the DSM-5 (Cosci &

Fava, 2016). Similarly, neither illness anxiety disorder nor somatic symptom disorder includes disease conviction as a diagnostic criterion, making the diagnostic criteria more representative of health anxiety than disease phobia (Cosci & Fava, 2019). Lastly, they further remarked two major ambiguities of the DSM system (Cosci & Fava, 2019). First, DSM-5 maintains the misleading concept of organic/functional dichotomy which assumes that if organic factors cannot be recognized, there should be psychological factors that may be able to fully explain the somatic symptomatology (Cosci & Fava, 2019). It is an oversimplification in contrast with the nature of the psychosocial approach of psychosomatic medicine (Cosci & Fava, 2019). Second, the DSM-5 classification system refers to abnormal illness behavior in all diagnostic rubrics, but it never provides a conceptual definition for it (Cosci & Fava, 2019). On the contrary psychosomatic medicine provides a clear definition of this latter concept (Cosci & Fava, 2019).

A revised version of the DCPR (DCPR-R) (Fava, Cosci, & Sonino, 2017) was proposed in 2017, under the light of the revision of the DSM nosography. The DCPR-R includes the diagnostic criteria for two additional syndromes: allostatic overload and hypochondriasis. The diagnosis of hypochondriasis was introduced since it was omitted in the DSM-5 classification and the diagnosis of allostatic overload was added since it reflects the cumulative effects of stressful experiences in daily life (Cosci & Fava, 2016). Thus, DCPR-R consists of a set of 14 psychosomatic syndromes clustered into four clinical domains: stress (i.e., allostatic overload), personality (i.e., type A behavior and alexithymia), illness behaviour (i.e., hypochondriasis, disease phobia, thanatophobia, health anxiety, persistent somatization, conversion symptoms, anniversary reaction, and illness denial), and psychological manifestations (i.e., demoralization, irritable mood, secondary somatic symptoms) (Fava, Cosci, & Sonino, 2017). The DCPR-R will be illustrated in relation to the four clinical domains to which they pertain (Figure 3).

Figure 3. Diagnostic Criteria for Psychosomatic Research Revised version (DCPR-R). Adapted from Fava, Cosci, and Sonino (2017)



2.1 Stress: Allostatic Overload

The role of life change and stress has evolved from the linear concept of homeostasis (i.e., the body's internal environment is held constant by the self-correcting "negative feedback" actions of its constituent organs) (e.g., Cannon, 1915; Seyle, 1956) to a more complex multivariate construct called "allostatic" (Sterling & Eyer, 1988; Mc Ewan & Stellar, 1993). The allostatic model (Sterling & Eyer, 1988) emphasizes the ability of the organism to achieve stability through change (Fava, Cosci, & Sonino, 2017). It encompasses the subordination of local feedbacks to the control by the brain providing a conceptual framework to explain the psychosocial modulation of physiology and pathology (Sterling & Eyer, 1988). In this vein, healthy functioning requests continual adjustments of the internal physiological milieu (Fava et al., 2010). Starting from these premises, McEwan and Stellar proposed the concept of allostatic load to explain the relationship between stress and the processes leading to disease (McEwan & Stellar, 1993). The allostatic load takes into consideration the cumulative effects of exposure to fluctuating or heightened neural or neuroendocrine responses resulting from repeated or chronic environmental challenges that an individual reacts to as being particularly stressful (Fava et al., 2019). It includes ordinary daily life events (e.g., job change, moving house), major challenges (e.g., death of a family member, severe economic difficulties) as well as physiological consequences of the resulting health damaging-behaviors (i.e., poor sleep or other aspects of circadian disruption, social isolation, lack of exercise, and poor diet) (Fava et al., 2019). The normal allostatic response is initiated by a stressor, sustained for an appropriate interval, and then turned off (Fava, et al., 2019). This normal response involves the balance of mediators that help to maintain homeostasis: norepinephrine, epinephrine, free cortisol, corticosterone, total and HDL cholesterol, glycosylated hemoglobin, IL-6, CRP, fibrinogen; waist–hip ratio; systolic and diastolic BP-seated/resting, and heart rate variability (McEwen & Wingfield, 2010). Conversely, allostatic load refers to the wear and tear that results from either too much stress or from inefficient management of allostasis which involves the sustained elevation and the dysregulation of mediators (Fava, et al., 2019). When the sustained elevation or dysregulation of mediators became stable, the individual perceives a state of toxic stress (McEwen & Wingfield 2010; Fava, et al., 2019). McEwen and Wingfield define allostatic overload as the transition to this extreme state of toxic stress (i.e., strong, frequent, or prolonged activation of the body stress response system in the absence of buffering factors or protection) in which daily life stresses are experienced by the individual as taxing or exceeding his/her coping skills (McEwen & Wingfield, 2010; Fava, et al., 2019).

Fava and colleagues remarked that the multiclausal model of allostatic overload

involves the modification of brain circuits through an adaptive plasticity process (Fava et al., 2019; Miller & Jones, 2014). Both experiences that lead to adaptation or to allostatic overload lead to a change in brain circuits and function epigenetically (Fava et al., 2019). During the stress exposure, brain circuits start to remodel the neural architecture to help individuals handle reality (Fava et al., 2019). A successful adaptation of the neural architecture builds a resilient circuit, whereas the persistence of these changes when the stress ends indicates a failed resilience (Fava et al., 2019).

First descriptions of allostatic load have been provided in pathophysiological terms by the use of its biological markers (e.g., McEwen, 2007; Shonkoff, Boyce, & McEwen, 2009; McEwen & Wingfield, 2010) and researchers have been tried to identify it using biological markers (Seeman, McEwen, Rowe, & Singer, 2001). The biological model of allostatic focuses on glucocorticoid dysregulation as part of a network of mediators involving autonomic, endocrine, metabolic, and inflammatory parameters (McEwen & Stellar, 1993; Seeman et al., 2001). A large array of biomarkers (e.g., resting systolic and diastolic blood pressure, waist-hip ratio, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides, glycosylated hemoglobin, fasting glucose, plasma C-reactive protein, fibrinogen, serum measures of interleukin-6, the soluble adhesion molecules E-selectin, intracellular adhesion molecule-1, levels of urinary epinephrine, norepinephrine, cortisol and a serum measure of the hormone dehydroepiandrosterone sulfate) (Seeman et al., 2001; Fava et al., 2019) was found to be better predictor of mortality and reduced physical functioning than individual biomarkers alone, even though several limitations emerged due to the complex nature of this network (Galen Buckwalter et al., 2016). Evidence for stress effects on health involve, for the most part, a correlational analysis of stress with occurrence of autonomie, cardiovascular, gastrointestinal, and immune system pathology (Fava et al., 2019). For each of these examples, there is evidence that acute or chronic stress contribute significantly as a risk factor to expression of disease (Fava et al., 2019). In this framework, most accurate indicators for the detection of allostatic overload are the symptoms reflecting behavioral manifestations of "toxic stress" in which the physiologic responses to stress exceed the coping resources contributing significantly as a risk factor to expression of disease (Fava et al., 2019; Mc Ewan & Stellar, 1993). For example, Holmes and Rahe focused on identifying major life events as a key component of the susceptibility to non-adaptive stress responses (Holmes & Rahe, 1967), however, they did not recognize the role of the individual's resources and cognition play in the stress response (Fava et al., 2019). Lazarus and Folkman emphasized the contribution of the cognitive component to the stress response (Lazarus & Folkman, 1984), but failed to include the influence of the physiological response to stress (Fava et. al., 2019). Cannon and Selye

considered only the physiological responses to stress and chronic stress (Cannon, 1932; Selye, 1956), but discounted the role of cognition in modulating this response (Fava et al., 2019).

In order to fill these gaps, Fava and colleagues introduced the clinimetric criteria for the diagnosis of allostatic overload in 2010 (Fava et al., 2010). The revised version was incorporated in the Diagnostic Criteria for Psychosomatic Research – Revised (DCPR-R) in 2017 (Fava, Cosci, & Sonino, 2017).

The clinimetric definition of allostatic overload refers to two criteria and is a trans-diagnostic categorization that may be applied regardless of the presence of psychiatric and/or medical conditions (Fava et al., 2019). The first criterion is concerned with the specification of the source of allostatic load (both life events and chronic stresses are allowed) and its contextual threat (i.e., judged to tax or exceed the individual coping skills when its full nature and full circumstances are evaluated) (Fava, Cosci, & Sonino, 2017; Fava et al., 2019). The second criterion deals with the clinical manifestations of the stress response which includes physical (e.g., difficulty falling asleep, lack of energy), psychological (e.g., generalized anxiety, sadness), and psychosocial symptoms (i.e., impairment in social and occupational functioning, in psychological well-being, specifically in terms of environmental mastery) (Fava et al., 2019).

The clinimetric criteria for the determination of allostatic overload have been used in several samples, such as the general population (Tomba & Offidani, 2012), patients in primary care (Piolanti et al., 2019), patients with cardiovascular disease (e.g., Porcelli et al., 2012; Offidani et al., 2013, Guidi et al., 2016), female outpatients with fibromyalgia (Leombruni et al., 2019), and breast cancer survivors (Ruini, Offidani, & Vescovelli, 2015).

2.2 Personality

The concept that personality traits can affect vulnerability to specific diseases was prevalent in the early phase of development of psychosomatic medicine, and was particularly influenced by psychoanalytic investigators, who believed that specific personality profiles underlay specific psychosomatic diseases (Fava, Sonino, & Wise, 2012). This hypothesis was not supported by subsequent research (Fava, Sonino, & Wise, 2012). Psychosomatic research has identified two personality constructs that can potentially affect general vulnerability to disease: type A behavior and alexithymia (Fava, Sonino, & Wise, 2012).

2.1 Type A Behavior

Type A behavior is an epidemiological construct introduced by the two cardiologists Meyer Friedman and Raymond H. Rosenman in 1959 to indicate a collection of behaviors observed in patients with heart conditions (Raymond & Rosenman, 1959). This constellation of behavioral was hypothesized to be a strong predisposing factor to Coronary Artery Disease (CAD) (Raymond & Rosenman, 1959; Matthews, 1982; Fabbri et al., 2007). Friedman and Rosenman defined the Type A behavior as "an action-emotion complex that can be observed in any person who is aggressively involved in a chronic, incessant struggle to achieve more and more in less and less time" (Friedman & Rosenman, 1974) (p. 67). Type A behavior is described as a set of overt and covert behaviors that are elicited from susceptible individuals by an appropriately challenging environment (Matthews, 1982). The two cardinal symptoms of the type A behavior are time urgency and free-floating (easily aroused) hostility (Allan, 2014). Time urgency is the persistent feeling that there is not or will not be sufficient time to accomplish the things that the patient feels should be done (Friedman, 1996). Consequently, the temporal tension deteriorates to a variant of free-floating hostility (i.e., irascibility, irritability, aggressiveness) if the patient becomes increasingly frustrated at not able to achieve his goals in the available period (Friedman, 1996). The others overt manifestations illustrated by Rosenman included: explosive, accelerated speech; a heightened pace of living; impatience with slowness; concentrating on more than one activity at a time; self-preoccupation; dissatisfaction with life; evaluation of the worthiness of one's activities in terms of numbers; a tendency to challenge and compete with others even in noncompetitive situations (Rosenman, 1978).

Moreover, Friedman described the covert characteristics of type A behavior (Friedman, 1996). He presumed that type A behavior has a psychological nucleus: "the time person harbors a feeling of insecurity or inadequate self-esteem ... Because of this underlying emotional inadequacy, the person suffering from it tries to ameliorate it by attempting to acquire as many achievements or to engage in as many activities as he or she possibly can." (Friedman, 1996) (pp. 25-26). This nucleus elicits other aspects of the type A person: he found it difficult to delegate to their peers (and especially their subordinates) various tasks and activities; he tends to set definite dates at which various activities should be accomplished; he is intolerant of even the trivial errors of omission and commission by others; he disbelief in altruism (Friedman, 1996). Conversely, these features are reduced or relatively absent in the so-called type B behavior subjects, who are described as characterized by relative absence of drive, ambition, sense of urgency, desire to compete, or involvement in deadlines (Friedman & Rosenman, 1959).

Compared to type B subjects, type A respond to challenging and competitive laboratory stressors with an increased sympathetic nervous system activity, resulting in a greater discharge of norepinephrine (Fava, Littman, & Halperin, 1988). Type A behavior appeared to be also associated with greater activity of the HPA axis, as suggested by higher daily average and peak adrenocorticotropic hormone values in type A than type B (Fava et al., 1988). However, the predisposing role of type A behavior in negative health outcomes is still controversial (e.g., Šmigelskas, Žemaitienė, Julkunen, & Kauhanen, 2014).

The clinimetric criteria for the determination of type A behavior were developed to allow this diagnosis also in non-cardiac conditions (Fava et al., 1995). According to the revised version of the DCPR, the diagnosis of type A behavior requires at least 5 of the 9 following characteristics (Criterion A): (1) excessive degree of involvement in work and other activities subject to deadlines; (2) steady and pervasive sense of urgency; (3) display of motor-expressive features indicating a sense of being under pressure of time; (4) hostility and cynicism; (5) irritability; (6) tendency to speed up physical activities; (7) tendency to speed up mental activities; (8) high desire for achievement and recognition; (9) high competitiveness (Fava, Cosci, & Sonino, 2017). DCPR-R criteria allowed to identify type A behavior in cardiac conditions as well as in consultation-liaison psychiatry setting (Galeazzi, Ferrari, Mackinnon, & Rigatelli, 2004), in patients with skin diseases (Picardi et al., 2005), functional gastrointestinal disorders (Porcelli, De Carne, & Fava, 2000), and cancer (Grassi, Sabato, Rossi, Biancosino, & Marmai, 2005). The prevalence rates ranged between 36.1% of subjects at risk of coronary heart disease and 10.8% of patients with non-cardiac diseases (Sirri et al., 2012).

2.2.2 Alexithymia

Peter Emanuel Sifneos coined the term alexithymia (from the ancient Greek stems: α = lack; λέξις = word; θυμός = mood) to describe the cognitive and affective style of patients suffering from two or more of the so-called "classical psychosomatic diseases" (e.g., rheumatoid arthritis and ulcerative colitis) (Sifneos, 1973). The literal translation of the term alexithymia is "no words for feelings" and it refers to a personality dimension concerned with difficulty in describing subjective feelings, an impoverished fantasy life as well as a cognitive style that is literal, utilitarian, and externally orientated (Taylor & Bagby, 2012). In 1976 Nemiah, Freyberger, and Sifneos defined alexithymia as a multifaceted interrelated construct composed by the following traits: (1) difficulty identifying feelings and distinguishing between feelings and the bodily sensations of emotional arousal; (2) difficulty describing feelings to other people; (3) constricted imaginal processes, as evidenced by a pau-

city of fantasy; (4) a stimulus-bound, externally oriented cognitive style (Nemiah, Freyberger, & Sifneos 1976).

It was hypothesized (Taylor, Bagby, & Parker, 1991) that the construct of alexithymia reflects a deficit in the cognitive processing and regulation of emotions involving three interrelated systems: neurophysiological (i.e., autonomic nervous system and neuroendocrine activation), motor-expressive (e.g., facial expressions, changes in posture and tone of voice), and cognitive-experiential (i.e., subjective awareness and verbal reporting of feeling states) (Taylor & Bagby, 2012). The Bucci's multiple code theory of emotional information processing further supported the idea that the alexithymic person presents deficit in the cognitive processing and emotion regulation being without certain cognitive, emotional, and sensory-motor schemas (Bucci, 2008; Taylor & Bagby, 2012).

Several self-report measures of alexithymia were developed such as the Schalling-Sifneos Personality Scale (SSPS) (Sifneos, 1973; Apfel & Sifneos, 1979), the alexithymia scale from items within the Minnesota Multiphasic Personality Inventory (MMPI) (Kleiger & Kinsman, 1980) as well as the 20-item Toronto Alexithymia Scale-II (TAS-20-II) (Bagby, Taylor, & Parker, 1994).

DCPR criteria were also developed to capture important pieces of information that would otherwise be lost using a self-rating scale (Fabbri et al., 2007). DCPR allows clinicians to observe and focus on the patient's emotional responses and therefore identify the relevant clinical features of alexithymia (Fabbri et al., 2007). The revised version of the criteria for the determination of the alexithymia were included in the DCPR-R and they were composed by one point (Criterion A) concerned with the presence of: (1) inability to use appropriate words to describe emotions; (2) tendency to describe details instead of feelings; (3) lack of a rich fantasy life; (4) thought content associated more with external events rather than fantasy or emotions; (5) unawareness of common somatic reactions that accompany the experience of a variety of feelings; (6) occasional but violent and often inappropriate outbursts of affective behavior (Fava, Cosci, & Sonino, 2017).

DCPR alexithymia was found to be linked to increased risk and worsened outcome of medical conditions in cardiovascular diseases (Lumley, Neely, & Burger, 2007), gastrointestinal disorders (Porcelli et al., 2003), cancer (De Vries, Forni, Voellinger, & Stiefel, 2012), and altered immune response to stress (Honkalampi et al., 2011).

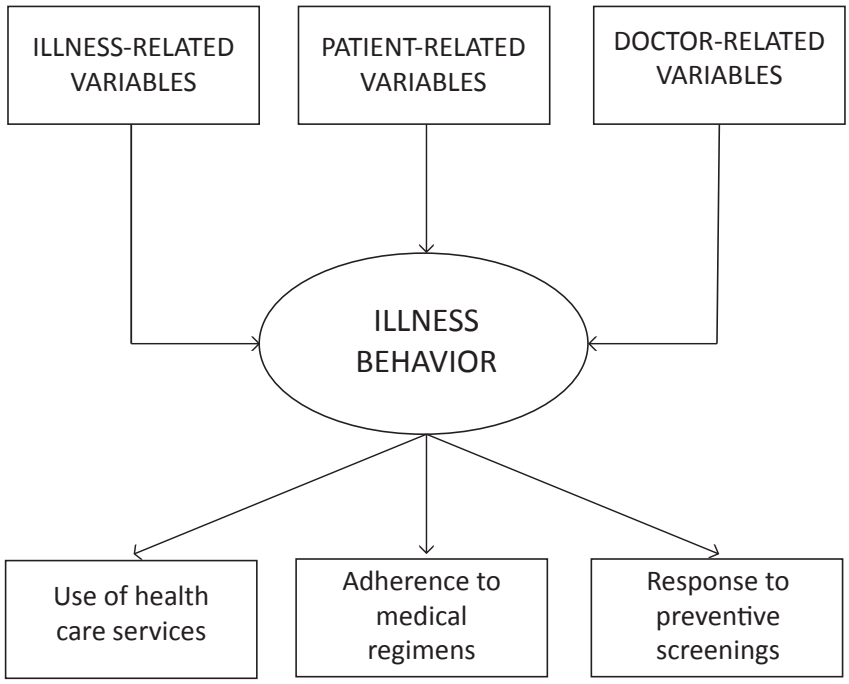
2.3 Illness Behaviour

The realm of Illness behaviour refers to the different ways in which patient perceived, evaluated, and acted (or not acted) his symptoms (Mechanic & Volkart, 1960). It was introduced in 1960 by David Mechanic and Edmund Volkart to de-

scribe the large variety of behavioral responses to a medical condition (Mechanic & Volkart, 1960). It identifies psychological and social dimensions that could affected such responses (Mechanic, 1995). According to Mechanic "Illness behavior refers to the varying ways individuals respond to bodily indications, how they monitor internal states, define and interpret symptoms, make attributions, take remedial actions and utilize various sources of informal and formal care" (Mechanic, 1995) (p. 1208). Thus, Illness behavior appears to be influenced by subjective, social, and cultural determinants and may vary from a subject to another one and within the same individual according to the situation and the kind of disease he has to cope with (Sirri & Grandi, 2012).

Sirri, Fava and Sonino described a unifying explanatory model of illness behavior (Sirri, Fava, & Sonino, 2013). As a major component of clinical encounters, illness behavior involves three main determinates: illness-related, patient-related, and doctor-related variables. In turn, these determinates influence health care services utilization, adherence to medical treatment, and response to preventive screenings (Figure 4).

Figure 4. Main determinants and consequences of illness behavior. Adapted from Sirri, Fava, and Sonino (2013)



In 1969, Issy Pilowsky introduced the term abnormal illness behavior (Pilowsky, 1969). He defined it as "the persistence of a maladaptive mode of experiencing, perceiving, evaluating and responding to one's own health status, despite the fact that

a doctor has provided a lucid and accurate appraisal of the situation and management to be followed (if any), with opportunities for discussion, negotiation and clarification, based on adequate assessment of all relevant biological, psychological, social and cultural factors" (Pilowsky, 1997) (p. 40).

Fava, Cosci, and Sonino proposed the domain of illness behavior in the revised version of the DCPR. (Fava, Cosci, & Sonino, 2017). DCPR-R illness behavior reflects both Pilowsky's concept of abnormal illness and Kellner's work derived from the use of the Illness Attitude Scale (IAS), suggesting that the differential diagnosis between hypochondriasis, disease phobia, thanatophobia, and health anxiety is worthy of clinical attention and may entail prognostic and therapeutic implications (Sirri & Fava, 2014). The DCPR-R illness behavior includes the diagnosis of eight psychosocial syndromes: hypochondriasis, disease phobia, health anxiety, thanatophobia, persistent somatization, conversion symptoms, anniversary reaction, and illness denial. Disease phobia and thanatophobia are components of hypochondriasis but they may also occur independently (Fava, Cosci, & Sonino, 2017).

2.3.1 Hypochondriasis

Warwick and Salkovskis defined hypochondriasis as the preoccupation with a belief in or fear of having a serious illness (Warwick & Salkovskis, 1990). This occurs without adequate organic pathology to account for the reaction and despite medical reassurance (Warwick & Salkovskis, 1990).

According to the DSM-IV, hypochondriasis encompasses affective, cognitive, and behavioral features (APA, 2000). The affective manifestations regard fears, worries, and concerns of illness relate to the idea of being seriously ill (APA, 2000). The cognitive features deal with alterations in both thought content (i.e., erroneous belief about having a disease) and process (i.e., misinterpretation of bodily symptoms) (APA, 2000). Disease conviction resistant to medical reassurance is the hallmark of hypochondriasis (APA, 2000). It is categorized as an overvalued idea, and it is defined in the DSM-IV as "an unreasonable and sustained belief that is maintained with less than delusional intensity… The belief is not one that is ordinarily accepted by other members of the person's culture or subculture" (APA, 2000) (p. 826). Behavioral manifestations are conceptualized as safety-seeking behaviors aimed at reducing fears of having a serious disease (Abramowitz et al., 2002). They include either reassurance seeking (e.g., requesting repeated medical examinations and laboratory tests; searching for medical information; checking individual's bodily functions and appearance) or avoidance of illness-related stimuli (e.g., avoidance of physical exertion because of fear of a heart attack) (Sirri & Fava, 2014).

The DCPR-R includes the DSM-IV diagnosis of hypochondriasis since it was

omitted in the DSM-5 classification (Fava, Cosci, & Sonino, 2017). DCPR-R provides four clinimetric criteria for the diagnosis of hypochondriasis: fears of having, or the idea of having, a serious disease based on misinterpretation of bodily symptoms (Criterion A); it persists despite adequate medical evaluation and reassurance, with opportunity for discussion and clarification (Criterion B); the duration of the disturbance is at least 6 months (Criterion C); the preoccupations cause marked distress and/or impairment in social and occupational functioning (Criterion D) (Fava, Cosci, & Sonino, 2017).

Fava, Cosci, and Sonino remarked that retaining hypochondriasis in the DCPR-R is important since specific psychotherapeutic strategies directed toward dysfunctional hypochondriacal cognitions have been developed and validated in randomized controlled trials (Fava, Cosci, & Sonino, 2017). Particularly, they were targeted to address resistance to reassurance, the key irrational beliefs of hypochondriasis which can be favorably modified (Cosci & Fava, 2016). Moreover, there is some evidence that hypochondriasis and illness worry are associated with a higher use of non-psychiatric health care resources than the other patients (e.g., Fink et al., 1999; Barsky, Ettner, Horsky, & Bates, 2001; Martin & Jacobi, 2006).

2.3.2 Disease Phobia

In 1971, Bianchi defined disease phobia as "a persistent, unfounded fear of suffering from a disease, with some doubt remaining despite examination and reassurance" (Bianchi, 1971) (p. 241).

He described disease phobia as "a variety of hypochondriasis" characterized by anxiety, inhibition of anger and low tolerance of pain (Fava & Grandi, 1991).

Pilowsky administered a standardized questionnaire to 100 cases of hypochondriasis and 100 control and he identified three dimensions of hypochondriasis: bodily preoccupation, disease phobia, and conviction of the presence of disease with non-response to reassurance (Pilowsky, 1967). Consistent with such a view, Kellner subdivides hypochondriasis into an unrealistic fear of disease (or illness phobia) and the conviction of having a disease (Kellner, 1985).

According to Fava, Cosci, and Sonino three clinical features differentiate disease phobia from hypochondriasis (Fava, Cosci, & Sonino, 2017). The first is specificity and longitudinal stability of symptoms: patients with disease phobia fear a specific disease and are unlikely to shift concerns to another disease or organ system (Sirri & Fava, 2014; Fava, Cosci, & Sonino, 2017). The second feature is the phobic quality of the fears, which tend to manifest themselves in attacks rather than in constant worry (Sirri & Fava, 2014; Fava, Cosci, & Sonino, 2017). The third element concerns behavioral manifestations: disease phobia avoidant behaviors concern both internal (e.g.,

somatic sensations, thoughts) and external (e.g., news, talks) illness-related stimuli (Sirri & Fava, 2014; Fava, Cosci, & Sonino, 2017). Conversely, reassurance-seeking or checking behaviors appear more frequently in hypochondriasis (Sirri & Fava, 2014; Fava, Cosci, & Sonino, 2017).

The revised version of the DCPR-R provided the clinimetric criteria for the diagnosis of disease phobia: persistent, unfounded fear of suffering from a specific disease, with doubts remaining despite adequate medical examination and reassurance (Criterion A); fears tend to manifest themselves in the form of attacks rather than in constant, chronic worries as in hypochondriasis (e.g., panic attacks may be an associated feature) (Criterion B); the object of fear does not change with time, and the duration of symptoms exceeds 6 months (Criterion C) (Fava, Cosci, & Sonino, 2017). Warwick and Marks reported the results of behavioral psychotherapy in a series of 17 cases suffering from disease phobia (Warwick & Marks, 1988). They showed the successfully used exposure to illness cues as well as prevention of reassurance, and highlighted that the phobic quality of the fear, typical of disease phobia, often leads to avoidance that can be faced with in vivo exposure (Warwick & Marks, 1988). On the contrary, Fabbri et and collegues noted that the constant fear of diseases characteristic of hypochondriacal patients often leads to doctor shopping behaviors and it may not respond to exposure (Fabbri et al., 2007). They purposed that the relationship of disease phobia to hypochondriasis could be similar to the one of panic disorder to generalized anxiety (Fabbri et al., 2007).

DCPR disease phobia showed a non-marginal prevalence in clinical populations since it was identified in a percentage of subjects varying from 2.2% in dermatological patients (Picardi et al., 2005) to 19% in consultation-liaison psychiatry patients (Galeazzi et al., 2004).

2.3.3 Thanatophobia

In 1928, Ryle described thanatophobia as the sense of dying or angor animi characterized by a sudden and irrational (i.e., without any medical reason) sense or conviction of being on the point of dying, not to be confused with the fear of eventual and inevitable death (Ryle, 1928). Kellner expanded the concept of thanatophobia, and he associated the conviction of dying soon with the fears of news with reminds of death, such as funeral and obituary notices (Kellner, 1986). More recently, Sirri and Fava defined thanatophobia as "a fear of dying characterized by attacks during which the individual feels that death is about to happen" and specified that "thanatophobic attacks may be observed in the setting of different psychiatric disorders, especially panic disorder, hypochondriasis, and disease phobia" (Sirri & Fava, 2014) (p. 16).

Primary thanatophobia was found less common than that which is secondary (Kellner, 1986). According to Sirri and Fava, in primary thanatophobia, attacks do not result from symptoms typical of another mental disorder and are accompanied by the avoidance of stimuli specifically related to the idea of death (Sirri & Fava, 2014). However, thanatophobia may occur also in the absence of other psychological symptoms (Fabbri et al., 2007).

Thanatophobia can be diagnosed using the clinimetric criteria of the revised version of the DCPR. The three DCPR-R clinimetric criteria are: at least 2 attacks in the past 6 months of impending death and/or conviction of dying soon, even though there is no objective medical reason for such fear (Criterion A); marked and persistent fear and avoidance of news that reminds of death (e.g., funerals, obituary notices) in which exposure to these stimuli almost invariably provokes an immediate anxiety response (Criterion B); avoidance, anxious anticipation, and distress interfere markedly with the level of functioning (Criterion C) (Fava, Cosci, & Sonino, 2017).

The following prevalence rates of DCPR thanatophobia were found in the medical setting: 8.2% in oncology patients (Grassi et al., 2004); 6.9% in transplanted patients (Grandi, et al., 2001); 4.9% in subjects in cardiac rehabilitation (Rafanelli et al., 2003); and 1.6% in patients with functional gastrointestinal disorders (Porcelli & Fava, 2000).

2.3.4 Health Anxiety

During the last decades, the term health anxiety has been a source of controversy (Sirri & Fava, 2014). Some authors (e.g., Ferguson, 2009) conceptualized it from a dimensional perspective in which the continuum of concerns about health ranges from mild to severe, including hypochondriasis as the most severe form (Sirri & Fava, 2014). According to this perspective, health anxiety and hypochondriasis are not distinct phenomena (Sirri & Fava, 2014). Other researchers suggested that hypochondriasis should be reclassified as an anxiety disorder because patients with hypochondriasis are characterized by high comorbidity with anxiety disorders and share common symptoms and underlying psychological mechanisms (Bailer et al., 2015).

According to Pilowsky, Kellner, and Fava health anxiety and hypochondriasis are two distinct clinical phenomena, with resistance to medical reassurance as the main feature that distinguishes them (Pilowsky, 1967; Kellner; 1986; Fava et al., 1995). In this view, hypochondriasis and health anxiety are considered qualitatively different, each deserving specific criteria of classification (Sirri & Fava, 2013).

Kellner reported that worry about illness (i.e., the tendency to be frightened by illness-related stimuli and by the idea of getting a nonspecific serious illness in the

future), concern about pain (i.e., the tendency to consider pain as an unequivocal sign of physical illness), and bodily preoccupation are the main manifestations of health anxiety (Kellner, 1986).

When health-anxiety individuals experience pain, their concerns activates affective and behavioral responses of fear and reassurance seeking (Sirri & Fava, 2014). Moreover, the cognitive style of subjects with high bodily preoccupation brings them to pay attention to illness-related information and tend to amplify their minor bodily sensations (Sirri & Fava, 2014). As a result, they find it difficult to think of something else when they experience bodily changes (e.g., increased heartbeat) or symptoms similar to those of the illnesses they heard or read about (Sirri & Fava, 2014).

The revised diagnosis of health anxiety is included in the DCPR-R. It encompasses worry about illness, concern about pain, and bodily preoccupation (Criterion A). Criterion B specifies that, in health anxiety, worries and fears readily respond to appropriate medical reassurance, even though new worries may ensue after some time (Fava, Cosci, & Sonino, 2017).

Health anxiety frequently occurs in oncology patients (37.7%) (Grassi et al., 2005) and was present in 11.6% of patients suffering from functional gastrointestinal disorders (Sonino et al., 2004) and in 7.7% of patients that underwent a heart transplant (Rafanelli, Roncuzzi, & Milaneschi, 2006).

2.3.5 Persistent Somatization

Somatization is a widespread clinical phenomenon that cuts across diagnostic categories, both psychiatric and medical type (Fabbri et al., 2007). However, there is an incomplete agreement among authors on the definition of somatization (Kellner, 1994).

The term somatization was introduced in 1925 by J. van Teslaar, the English translator of the Wilhelm Stekel's book "Peculiarities of behavior: Wandering mania, dipsomania, kleptomania, in pyromania and allied impulsive acts". Teslaar translated by the neologism ''somatization'' the German word ''organsprache'' (organ-speech), a notion issued from Stekel and Adler, evoking the hereditary susceptibility of an organ to be diseased (Marin & Carron, 2002). Teslaar defined somatization as "conversion of emotional states in physical symptoms'' (Marin & Carron, 2002).

Katon et al. defined it as "an idiom of distress in which patients with psychosocial and emotional problems articulate their distress primarily through physical symptomatology (Katon et al., 1982).

Kleinman and Kleinman define it as "the expression of personal and social distress in an idiom of bodily complaints with medical help-seeking" (Kleinman & Kleinman, 1986). Ford labeled it as the use of somatic symptoms for psychological pur-

poses (Ford, 1986). Lipowski referred at it "as a tendency to experience and communicate psychological distress in the form of physical symptoms and to seek medical help for them" (Lipowski, 1987) (p. 161).

Kissen purposed a board definition of somatization in accordance with one of the criteria from the DSM-III-R (APA, 1987) diagnosis for undifferentiated somatoform disorders (Kissen, 1994). In this way, somatization indicated one or more physical complaints (e.g., fatigue, gastrointestinal or urinary complaints) and either (1) appropriate evaluation uncovers no organic pathology or pathophysiologic mechanism (e.g., a physical disorder or effect of injury) to account for the physical complaints, or (2) when there is related organic pathology, the physical complaints or resulting social or occupational impairment are grossly in excess of what would be expected from the physical findings (Kissen, 1994).

Kissen highlighted that there was a close relationship and a blurred boundary between psychosomatic syndromes and the illnesses diagnosed as somatization disorders according to the DSM-III-R findings (e.g., fibromyalgia, abdominal pain, nonnuclear dyspepsia, urethral syndrome, and irritable bowel syndrome) (Kissen, 1994). Moreover, he observed that patients with psychosomatic syndromes were characterized by the tendency for clustering of syndrome (i.e., a person with a psychosomatic syndrome is at risk of acquiring another), personality trait associated with the "patient status" (i.e., people who sought treatment), psychiatric comorbidity, characteristic pattern of physiological response to stress, and a lower pain threshold (Kissen, 1994).

The DCPR diagnosis of persistent somatization was developed to overcome some conceptual flaws of the DSM-IV diagnosis of somatization disorder, which appeared to be rarely used and of limited utility in clinical settings, mostly because of its very restrictive criteria (Sirri et al., 2007).

The revised criteria of the DCPR identifies persistent somatization as referred to patients in whom somatic symptoms have clustered (Fava, Cosci, & Sonino, 2017). Fava, Cosci, and Sonino explained the clustering of functional medical disorders as probably due to an enhanced general sensitivity to pain and discomfort or altered brain-body interactions (e.g., findings of altered brain-gut interactions, inflammation, and visceral hypersensitivity in irritable bowel syndrome; distinction between 'functional' and 'organic' symptoms obtained via advanced brain imaging methods) (Fava, Cosci, & Sonino, 2017).

Criterion A of DCPR-R persistent somatization was determined by the presence of functional medical syndromes (fibromyalgia, chronic fatigue, esophageal motility disorders, nonulcer dyspepsia, irritable bowel syndrome, atypical chest pain, overactive bladder) whose duration exceeds 6 months causing distress, seeking medical care or resulting in impaired quality of life (Fava, Cosci, & Sonino, 2017). Criterion

B refers to the presence of symptoms of autonomic arousal involving different organ systems (e.g., palpitations, tremor, flushing, sweating), and/or exaggerated side effects from medical therapy, indicating the low threshold of pain sensation, and/or high suggestibility (Fava, Cosci, & Sonino, 2017).
Some studies conducted in medical settings have applied the DCPR system to assess persistent somatization. The prevalence of the syndrome was 1.5% in heart-transplanted patients (Grandi et al., 2001), 21% in endocrine patients (Sonino et al., 2004), 38% in a sample of subjects suffering from functional gastrointestinal disorders (Porcelli, De Carne, & Fava, 2000).

2.3.6 Conversion Symptoms

Conversion symptoms had an irregular conceptual evolution (Espirito-Santo & Pio-Abreu, 2009). It started from the concept of hysteria and ended with the DSM somatization, dissociative, and conversion disorders (Espirito-Santo & Pio-Abreu, 2009). The term hysteria (from the ancient Greek word ὑστέρα = uterus) was coined by Hippocrates and used to describe women with abnormal movements of the uterus (Madva, Ross, & Cooper, 2019). In the nineteenth century, Charcot and Freud used the term hysteria to theorize a connection between repressed negative affect and neurologic symptomatology (Madva, Ross, & Cooper, 2019). Freud was particularly influenced by the case of Anna O. and postulated that Anna O.'s psychological distress and previous trauma were "converted" into her neurologic symptoms, a phenomenon he ultimately described as hysterical conversion (Breuer & Freud, 1895). Subsequently, the term conversion was used by the psychiatrists to indicate a medical syndrome that imply a lack of biological etiology (Madva, Ross, & Cooper, 2019). Even though, there are no evidence supporting the concept of neurotic conversion (e.g., Lipowsky 1985; Fava & Sonino, 2002) the term conversion has been in common use in psychiatry and clinical psychology until today (Madva, Ross, & Cooper, 2019). In the medical literature, conversion symptoms are the relatively persistent losses or alteration in voluntary motor or sensory functioning that cannot be explained by known organic disorders or pathophysiologic mechanism (Lazare, 1981). Examples includes paralysis, abnormal movements, aphonia, hypoesthesia, sensation of coldness or warmth, blindness and deafness (Lazare, 1981). Similarly, conversion disorder in the DSM may have neurological symptoms, including weakness, numbness and events resembling epilepsy or syncope, which can be positively identified as not being due to recognized neurological disease (Stone et al., 2011).
On the other hand, Engel conceptualized a different meaning of a conversion disorder and providing a set of more stringent criteria than DSM, which lead to a biopsychosocial definition of conversion symptoms (Engel, 1970). Engel's definition

involving features such as ambivalence, histrionic personality, and precipitation of symptoms due to psychological stress of which the patient is unaware (Engel, 1970). Engel's criteria were incorporated in the three DCPR-R diagnostic criteria for conversion symptoms (Cosci & Fava, 2019). Criterion A encompasses the presence of one or more symptoms or deficits affecting voluntary motor or sensory function characterized by lack of anatomical or physiological plausibility, absence of expected physical signs or laboratory findings or inconsistent clinical manifestations (Fava, Cosci, & Sonino, 2017). Moreover, criterion A allows to consider the presence of autonomic arousal or persistent bodily symptoms (Fava, Cosci, & Sonino, 2017). If these features are present, conversion symptoms should be prominent and cause distress or seeking medical care or impaired quality of life (Fava, Cosci, & Sonino, 2017). Criterion B requires that an appropriate medical evaluation uncovers no organic pathology to account for the physical complaints (Fava, Cosci, & Sonino, 2017). Criterion C includes the Engel's definition of somatization: (1) Ambivalence in reporting of symptoms; (2) histrionic personality features (3); precipitation of symptoms by psychological stress (4); history of similar physical symptoms experienced by the patient, observed in someone else, or wished on someone else (Fava, Cosci, & Sonino, 2017).

DCPR conversion symptoms were found in 5% of subjects suffering from functional gastrointestinal disorders (Porcelli, De Carne, & Fava, 2000) and in in 7% of subjects on their first episode of myocardial infarction (Ottolini, Modena, & Rigatelli, 2005).

2.3.7 Anniversary Reaction

The relationship between anniversaries and the onset or exacerbation of illness has been of long-standing clinical interest (Sirri et al., 2007). Sándor Ferenczi in his paper on "Sunday neuroses", firstly described symptom oscillations that occur on a particular day of the week. These "nervous conditions had developed mostly … on a certain day of the week, and had then regularly recurred." (Ferenczi, 1919) (p. 174). Ferenczi reported that the periodic symptoms of his patient returned mostly on Sundays and consisted of headaches, depressions, gastrointestinal disturbances, and oversleeping (Ferenczi, 1919).

In two case reports, Jhosepine Hilgard observed that "symptoms in a parent may be precipitated when the parent's child reaches the age at which the parent had a traumatic episode in childhood" (Hilgard, 1951) (p. 73). She labeled these periodic symptoms as anniversary reactions and described them as related to precipitating trigger situations such as birthday, death day, or other fixed dates (Hilgard, 1951). In a subsequent paper, Hilgard and Newman extended the precipitating trigger including the age of the adult patient as it coincides with the age of the parent who

died during the patient's childhood (Hilgard & Newman, 1959). Engel outlined the links between anniversaries and the giving up-given complex in which patients are prone to revive unpleasant feelings experienced in the past (Engel, 1966; 1975). Similarly, the concept of nemesis (Chapman, 1977) (i.e., the patient believes he is destined to repeat in his life the pattern of a significant other person's life which ended in tragedy or catastrophe) is closely related to anniversary reactions (Fabbri et al., 2007).

According to the DCPR-R criteria, anniversary reaction is a form of somatization or conversion specifically linked to an anniversary (Cosci & Fava, 2019). It includes three criteria: symptoms of autonomic arousal, functional syndromes or conversion (Criterion A), with no organic pathology to account for physical symptoms (Criterion B), began when the patient reached the age, or on the occasion of the anniversary, when a parent or very close family member developed a life-threatening illness and/or died (Criterion C) (Fava, Cosci, & Sonino, 2017). The patient should be unaware of such association (Fava, Cosci, & Sonino, 2017).

The prevalence of DCPR criteria for anniversary reaction were found to be low: 0.7% in patients undergoing heart transplantation presented with anniversary (Grandi et al., 2001), and 0.5% in patients with functional gastrointestinal disorders (Porcelli, De Carne, & Fava, 2000).

2.3.8 Illness Denial

The concept of denial derived from psychoanalytic theory (Fabbri et al., 2007). Sigmund Freud originally used the term denial ("Verleugnung" translated as "disavowal" by James Strachey) in regard to the disavowal of reality in psychotic patients (Freud, 1924). Anna Freud described denial of external realities as a commonly ego-defense mechanism used by children to deal with unpleasant aspects of outer reality (Freud, 1961). Vaillant, Sjöbäck, and Fenichel described denial in adults as an immature and pathological ego-defense mechanism observed in psychotic patients (Vaillant, 1971; Sjöbäck, 1973; Fenichel, 1979). On the contrary, Sperling suggested to differentiate the concept of denial in two forms: a first form of complete rejection of reality; a second form of denial which acts as a defense against without leading to a complete rejection of this perception (Sperling, 1958).

In the cognitive framework, Dorpat's theory of denial argued that denial is a process of cognitive arrest (Dorpat, 1983). The process of arrest results from the preconscious or conscious appraisal of disturbing stimuli (i.e., danger or trauma) associated with negative affects (i.e., subjectively painful or distress) (Dorpat, 1983). As part of the ensuing cognitive arrest, focal attention is shifted from disturbing stimuli to less disturbing stimuli such as fantasies or ideas (Dorpat, 1983). This ren-

ders the subject unable to think and act rationally about the object of his denial (Dorpat, 1983). Horowitz described the denial following the completion tendency theory (i.e., patients seek to integrate outer reality and internal cognitive schemas) (Horowitz, 1983). In this context, new external information is held in memory stores until this integration has taken place (Horowitz, 1983). When outer reality such as a danger or trauma cannot be altered, a change of internal cognitive schemata is required through the use of inhibiting controls (Horowitz, 1983). These controls allow storing information without excessive levels of emotion or retraumatization (Horowitz, 1983). Therefore, the denial results from the excessive or prolonged use of inhibiting controls (Horowitz, 1983).

According to Pilowsky's abnormal illness behavior model (Pilowsky 1969; 1997), illness denial represents a psychological response to patient's own physical illness covering several phenomena (Fabbri et al., 2007; Sirri & Grandi, 2013). Denial of physical illness may range from an unrealistic optimism to the complete denial of disease (Pilowsky, 1997).

Illness denial has been described in a variety of clinical domains, especially in patients with cancer (Galeazzi et al., 2004), diabetes (Garay-Sevilla, Malacara, Gutierrez-Roa, & Gonzalez, 1999), renal (Goldbeck, 1997), cardiovascular (Young et al., 1991), and neurological diseases (Goldbeck, 1997). Illness denial is considered maladaptive when it results in a non-adherence to therapeutic regimens, delay in undergoing medical examinations, or the adoption of unhealthy behaviors (Sirri & Grandi, 2013). In these cases, denial may worsen the course of disease, may lead to counterphobic behavior or, in the case of healthy subjects, may represent a risk factor for unsafe health habits (Fabbri et al., 2007).

Since illness denial has been neglected by DSM classifications, distinctive criteria for the recognition of denial in physical illness have been provided by the DCPR classification (Fava et al., 1995).

DCPR-R Illness denial allows identifying patients who do not acknowledge the presence or severity of their illness (Fava, Cosci, & Sonino, 2017). Criterion A is aimed to investigate the presence of persistent denial as a reaction to the physical illness, and Criterion B investigates if the patient has been discussed and clarified with physicians his/her medical situation and management with an adequate appraisal (Fava, Cosci, & Sonino, 2017).

DCPR criteria for illness denial identified this phenomenon in several clinical domains (Fava, Cosci, & Sonino, 2017). It was found in: 2% of dermatological inpatients (Picardi et al., 2005); 5% of subjects who underwent heart transplantation (Grandi, Sirri, Tossani, & Fava, 2011); 9% of women with breast cancer (Grassi et al., 2005); and 29% of subjects in consultation-liaison psychiatry patients (Galeazzi et al., 2004).

2.4 Psychological Manifestations

Current emphasis in psychiatry and clinical psychology is directed primarily towards the assessment of symptoms resulting in syndromes identified by DSM criteria (Fava, Sonino, & Wise, 2012). However, psychosomatic principles cover the concept that also psychological symptoms that fail to reach the threshold of a psychiatric disorder may equally affect the quality of life and entail pathophysiological and therapeutic implications (Fava, Sonino, & Wise, 2012; Fava, Cosci, & Sonino, 2017). Similarly, psychological symptoms could only partially account for the unexplained medical disorder (Fava, Cosci, & Sonino, 2017) and DCPR classification system goes beyond the "misleading and dangerous assumption that if organic factors cannot be identified there must be psychological reasons which fully explain the somatic symptomatology" (Fava, Cosci, & Sonino, 2017) (p. 20).
According to these principles, the DCPR-R allows to diagnose two psychological manifestations, demoralization and irritable mood, that DSM nosography does not take into account (Fava, Cosci, & Sonino, 2017).

2.4.1 Demoralization

Frank introduced the term demoralization to describe a cluster of symptoms characterized by a feeling of subjective incompetence, impotence, isolation, and despair resulting "from persistent failure to cope with internally or externally induced stresses that the person and those close to him expect him to handle" (Frank, 1974) (p. 271). According to the author, the inability to cope was identified "as feelings of being overwhelmed and defeated by one's circumstances and of being unable to effectively engage in problem-solving and perform tasks" (Frank, 1974) (p. 271). The persistence of a sense of subjective incompetence may result in the appearance of severe distress (Frank, 1974). Frank purposed that this state of subjective incompetence characterized psychotherapy clients seeking treatment who had exhausted personal resources and were no longer able to cope with their problems (Frank, 1974).
Engel and Schmale subsequently recognized a state that appears to be acute demoralization in the "giving up-given up complex", a psychological state which may precede an illness (Engel, 1963; Schmale, 1972). They indicated a complex state that included both helplessness and hopelessness and they noted a failure in the coping ability (Engel, 1963; Schmale, 1972). The inability to cope was described by Engel as a sense of psychological impotence in which previously used strategies, whether psychological or social, seem no longer effective in dealing with changes in the environment (Engel, 1963). Individuals who had "given up" demonstrated certain

common characteristics which included feelings of incompetence and being out of control, feeling "at the end of their tether", a loss of gratification from roles, a sense of disruption in continuity with the past and future, and the recall of previous helpless situations (Engel, 1963; Schmale, 1972; Stephenson, 1991). Engel and Schmale hypothesized that in the presence of vulnerability to organic diseases, the giving up-given up complex could be able to alter and compromise individual's biological economy and consequently disrupt individual's ability to counterbalance pathogenic processes (Schmale & Engel, 1967).

Subsequently, Sweeney et al. provided a differentiation between helplessness and hopelessness (Sweeney et al., 1970). Helplessness entailed a "feeling of being abandoned where loss of gratification is perceived as caused by external events or objects and cannot be regained by active self-intervention. Hopelessness was hypothesized to develop instead when the individual feels that he/she alone is responsible for the loss and that there is nothing that he or anyone else can do to overcome it." (Sweeney et al., 1970) (p. 674).

De Figueiredo and Frank further elaborated the demoralization syndrome and defined it as a combination of distress and subjective incompetence (De Figueiredo & Frank, 1982; De Figueiredo, 1993).

Fava et al., provided the DCPR definition of demoralization integrating Frank's demoralization syndrome as well as Schmale and Engel's giving up-given up complex (Fava et al., 1995; Cosci & Fava, 2019).

The DCPR-R criteria of demoralization include helplessness (i.e., feeling state characterized by the perception of being unable to cope with some pressing problems the individual maintains the capacity to react but lacks adequate support) and hopelessness (i.e., the individual feels he/she alone is responsible for the situation, and there is nothing he/she or anyone else can do to overcome the problem). Additional aspects are the prolonged period of demoralized states lasting for longer than one month and the feeling state should be prolonged and generalized (Fava, Cosci, & Sonino, 2019).

Demoralization and major depression, although overlapping, can be differentiated on clinical grounds (Porcelli & Todarello, 2012; Fava, Cosci, & Sonino, 2017). Depressed patients show a reduction of experiencing enjoyment, motivation, and drive, whereas demoralized patients are unable to acknowledge anticipatory pleasure because of inhibition in his or her initiative, but consummatory pleasure is unaffected (Porcelli & Todarello, 2012). However, hopelessness/giving up is more likely to be linked to depressive illness and may provide a severity connotation to the diagnosis of major depressive disorder (Fava, Cosci, & Sonino, 2017). Both hopelessness and helplessness have found to be related to the activity of the serotonergic and noradrenergic system disorder (Fava, Cosci, & Sonino, 2017).

In the medical context, DCPR demoralization showed high prevalence rates in all medical conditions (30%), and low frequency in healthy subjects (2–5%) (Tecuta et al., 2014). A preliminary study reported that 15% of a psychiatric sample suffering from the syndrome (Chaturvedi & Goswami, 2012) and in cardiology, has been identified as a prodromal symptom of cardiac events (Fabbri et al., 2007).

2.4.2 Irritable Mood

Irritability describes proneness to anger (Vidal-Ribas et al., 2015). Snaith and Taylor provided the first definition of irritability for use in the context of psychopathology: "irritability is a feeling state characterized by reduced control over temper which usually results in irascible verbal or behavioral outbursts, although the mood may be present without observed manifestation. It may be experienced as brief episodes, in particular circumstances, or it may be prolonged and generalized. The experience of irritability is always unpleasant for the individual and overt manifestation lacks the cathartic effect of justified outbursts of anger" (Snaith & Taylor, 1985) (p. 128).

However, considerable confusion existed in distinguishing irritability from anger, aggression, and other related constructs (Toohey & DiGiuseppe, 2017). In the DSM-5 irritability ranges across 15 disorders included in mood disorders, addictive disorders, personality disorders, and more (Toohey & DiGiuseppe, 2017). The terms irritability is described in various ways across DSM-5 disorders (e.g., mood [that] can be irritable, unexplained irritability, and irritable behavior) and it is unclear what discriminates unexplained irritability from irritability or irritability from irritable mood, and these latter terms are often used interchangeably (Toohey & DiGiuseppe, 2017).

On the contrary, the DCPR system provides a clear definition of irritability consistently with those of Snaith and Taylor (Fabbri et al., 2007). Moreover, Fava clarified that inward and outward irritability, hostility, aggression, and anger are similar but distinct phenomena from irritability (Fava, 1987). Aggression implies destructive or punitive behavior directed towards other persons, whereas hostility is a personality characteristic that, unlike irritability, requires an object (Fava, 1987). Irritable mood can represent a mood state independent of other anxious (Fava et al., 1993) or depressive disorders (Fava, 1998), even though irritability may be a secondary manifestation of all major psychiatric disturbance as well as DCPR-R type A behavior (Fabbri et al., 2007).

DCPR-R provides two main criteria to identify irritable mood (Fava, Cosci, & Sonino, 2017). First criterion requires the presence of a feeling state characterized by irritability which may be experienced as brief episodes or may be prolonged and

generalized; it requires an increased effort of control over temper or results in irascible verbal or behavioral outbursts (Fava, Cosci, & Sonino, 2017). Second criterion concerns the quality of the experience of irritability. It should be always unpleasant, and its overt manifestations lack the cathartic effect of justified outbursts of anger (Fava, Cosci, & Sonino, 2017).

Concerning irritable mood in the medically ill, Fava described different pathways linking irritability to physical illness (Fava, 1987). Irritability and other related mood states seemed to be involved in the development of medical diseases (Miller et al., 1996) even though affective responses are based on each patient's psychological assets and liabilities (Fava, 1987). Irritability can be induced by medical illness and may represent a psychological response to hospitalization, disability, pain, treatments, and diagnostic procedures (Fava, 1987). Otherwise, irritability can be activated by stressful conditions, including returning to work, social, and family reintegration (Battaglia et al., 2018).

Hypertension, atherosclerosis, atrial fibrillation, and coronary heart disease was found to be related with hostility, and more particularly, its cynical component was found to be associated with increased risk of cardiovascular diseases and myocardial infarction, especially in younger patients (Fabbri et al., 2007). Unexpressed anger has been found to be a predisposing factor to cancer, chronic pain, and functional somatic symptoms (Fabbri et al., 2007). Increased levels of irritability have been observed in gastrointestinal disorders (Welgan, Meshkinpour, & Ma, 2000); in particular, anger was found to influence colon activity and trait anger reactivity predicted the severity of FGID (Welgan, Meshkinpour, & Ma, 2000). Further, hostility and irritability have been addressed as predictors of unhealthy behaviors, such as smoking and pathological alcohol consumption (Miller et al., 1995).

In patients recruited from medical settings, prevalence rates of DCPR irritable mood were found to be 10-15%, including patients with myocardial infarction, heart transplantation, functional gastrointestinal disturbances, cancer, and skin diseases (Porcelli & Guidi, 2015), whereas in patients with kidney transplant recipients and in patients with endocrine disorders were found to be to 31% and 46% respectively (Sonino et al., 2004; Battaglia et al., 2018).

2.4.3 Somatic Symptoms Secondary to a Psychiatric Disorder

The concept of comorbidity was proposed by Feinstein in 1970 to denote cases in which a "distinct additional clinical entity" occurs during the clinical course of a disease (Feinstein, 1970). Comorbidity between medical and mental disorders is the rule rather than the exception (Šprah, Dernovšek, Wahlbeck, & Haaramo, 2017). More than 68% of adults with a mental disorder reported having at least one general

medical disorder and 29% of those with a medical disorder had a comorbid mental health condition (Kessler et al., 2004; Kessler & Merikangas, 2004). Several findings have shown an increased risk for various physical diseases in patients with mental disorders such as human immunodeficiency virus, impaired lung function, obstetric complications, stroke, myocardial infarction, hypertension, obesity, or diabetes mellitus (de Hert et al., 2011). On the other hand, many medical disorders increase the risk for mental disturbances or worsening of existing symptoms (Iacovides & Siamouli, 2008). There is evidence that having a mental disorder is a risk factor for physical disorder and vice versa (Šprah et al., 2017). For example, having a physical illness is one of the strongest risk factors for depression; and depression is also a risk factor for physical illness (Šprah et al., 2017). In particular, the diagnosis of major depression has emerged as an extremely relevant source of comorbidity in medical disorders (Fava, Cosci, & Sonino, 2017). Depression was found to increase the susceptibility to medical illness sustaining the inflammatory state, and thus mediating the risk for cardiovascular and neoplastic disease (Fava, Cosci, & Sonino, 2017). Moreover, depression was found to be a marker of disease severity in Cushing's disease (Rafanelli, Sirri, Grandi, & Fava, 2013) and to be associated with higher rates of somatic symptoms in the medically ill (Katon, 2003). Association between chronical medical disorder and depression was found to affect social functioning, leading to increased health care utilization (Katon, 2003) as well as to have a relevant impact on the compliance with medical treatment (DiMatteo, Lepper, & Croghan, 2000). Similarly, the relationship between anxiety disorders and medical disorders were also found to entail important clinical implications (e.g., Fava et al., 2010). However, psychiatric disorder in the course of the medical disease is substantially different from that can be found in psychiatric settings in terms of clinical characteristics, response to treatment, and prognosis (Fava, Cosci, & Sonino, 2017).

In this context, the revised DCPR diagnosis of somatic symptoms secondary to a psychiatric disorder allows physician to acknowledge the hierarchical relationship between psychiatric disorders, (particularly mood and anxiety disturbances) and to formulates the hypothesis that somatic symptomatology may remit upon the remission of the psychiatric disorder (Fava, Cosci, & Sonino, 2017).

DCPR-R somatic symptoms secondary to a psychiatric disorder is described by the main feature of the presence of somatic symptoms that cause distress, seeking medical care or impaired quality of life (Criterion A). Somatic symptoms should be unexplained by an appropriate medical evaluation (Criterion B) and a psychiatric disorder (which includes somatic symptoms within its manifestations) should precede the onset of somatic symptoms (e.g., panic disorder preceding cardiac symptoms) (Fava, Cosci, & Sonino, 2017).

The prevalence of functional somatic symptoms secondary to psychiatric disorders

has been found in the range of 30–45% in high health care users (Porcelli & Rafanelli, 2010); ranging between 75% in functional gastrointestinal disorder subjects; 90% in psychiatric consultation subjects (Porcelli & Rafanelli, 2010).

3 The Framework of the PAINMIG Study

3.1 The Concept of Euthymia

In the past decades, psychosomatic research has fully recognized the need to expand the spectrum of psychological assessment including consideration of function in daily life, productivity, performance of social roles, intellectual capacity, emotional stability, and well-being as crucial part of clinical investigation and patient care (Fava, Belaise, & Sonino, 2010). In this line, a growing body of research has highlighted that psychological well-being plays a buffering role in coping with stress and has a favorable impact on the disease course (e.g., Pressman & Cohen, 2005; Ryff, 2014).

In recent years, Giovanni A. Fava and Per Bech expanded the concept of well-being (e.g., Ryff, 1989; Firsch, 2006; Seligman & Csikszentmihalyi, 2000; Rashid & Seligman, 2018) through the introduction of the notion of euthymia (Fava & Bech, 2016). The term euthymia derived from the ancient Greek and results from the combination of "εὖ" meaning "well" and "θυμός" meaning "soul, emotion". Dêmocritus was the first who provided a definition of euthymia as a state of quiet satisfaction, including a balance of emotions enabling a person to defeat their own fears (Dêmocritus, DK B 181). Seneca translated the Greek term of euthymia with the Latin concept of "tranquillitas animi", a state of internal calm and contentment leading to psychological well-being (Seneca, 1900). Despite this, the concept of euthymia has been historically tackled in negative terms to describe a patient who no longer met the criteria for a psychiatric disorder (Fava, Cosci, Guidi, & Tomba, 2017; Fava & Bech, 2016).

Marie Jahoda was the first who approached this concept in clinical terms in her book on positive mental health (Jahoda, 1958). She questioned the viewpoint of euthymia as a state corresponding to the mere absence of symptoms and outlined six specific criteria for its positive definition (Jahoda, 1958):

a. autonomy (regulation of behavior from within);
b. environmental mastery;
c. satisfactory interactions with other people and the milieu;
d. the individual's style and degree of growth, development or self-actualization;
e. the attitudes of an individual toward his/her own self (self-perception/acceptance);

f. the individual's balance and integration of psychic forces (flexibility) (adapted from Fava, 2016).

Autonomy refers to conscious discrimination by the individual of accepting or rejecting the environmental factors being independent of social influences (Jahoda, 1958). Environmental mastery encompasses the efforts to achieve success in some social roles and the ability to have positive social relationships and to solve problems in an efficient way (Jahoda, 1958). Satisfactory interactions with other people describe positive interpersonal and social functioning (Jahoda, 1958). Individual's style and degree of growth refers to what a person does with himself over a certain period of time, and his trajectories of positive human development (Jahoda, 1958). Self-perception includes a positive connotation in one's judgment, ability, and power (Jahoda, 1958). Flexibility refers to the balance of psychic forces that allow a unifying outlook on life, and to resistance to stress (Jahoda, 1958).

Thereafter, Carol Ryff derived her model of psychological well-being from Jahoda's first five dimensions of positive functioning and introduced a method for their assessment, the Psychological Well-Being scales (PWB) (Ryff, 1989; Ryff, 2014). PWB encompasses six dimensions: autonomy, environmental mastery, purpose in life, personal growth, self-acceptance, and positive interpersonal relationships (Ryff, 2014). Taken together, these dimensions characterize individual's optimal functioning (Ryff, 2014). Autonomy refers to independence, self-determination and the ability to resist social pressure to think or act in certain ways (Ryff, 2014). Environmental mastery consists of taking advantage of environmental opportunities, participating in work and familial activities, and possessing a sense of competence in managing everyday activities (Ryff, 2014). Personal growth is related to being open to new experiences, being capable of facing challenges and tasks at different periods of life and considering the self as growing and expanding over time (processes of self-realization) (Ryff, 2014). Positive relations with others consist of possessing warm and trusting relationships with others, being capable of strong empathy, affection, and intimacy (Ryff, 2014). Purpose in life includes the achievement of goals, intentions, and a sense of direction which contributes to the feeling that life is meaningful (Ryff, 2014). Self-acceptance consists of possessing a positive attitude toward the self, recognizing various parts of oneself, such as one's good and bad qualities, feeling self-confident and accepting one's past life and all its positive and negative experiences (Ryff, 2014).

In 2016, Fava and Bech purposed the euthymia as a new indicator of well-being to apply in the study of human wellness (Fava & Bech, 2016). They remarked that Ryff missed the sixth component of Jahoda's model: the flexibility (Fava & Bech, 2016). It concerns the individual's balance of psychic forces and it is strictly related to the concept of euthymia (Fava & Bech, 2016). They argued that flexibility

allows "a unifying outlook on life which guides actions and feelings to shape the future accordingly, and resistance to stress (resilience and anxiety or frustration tolerance)" (Fava & Bech, 2016) (p. 2). Thus, flexibility makes possible to adjust the psychological dimensions of well-being in relation to the changing needs (Fava & Bech, 2016). They also outlined more recent studies on the theme of flexibility (e.g., Tyrer, Seivewright, Ferguson, & Tyrer, 1992; Kashdan & Rottenberg, 2010). These works have shown that an absence of flexibility is likely to yield depression, anxiety, and more particularly the general neuroticism syndrome (i.e., the general tendency to experience negative emotions more frequently, intensely, and readily, for more enduring periods of time) (Kashdan & Rottenberg, 2010). This latter syndrome was shown to be associated with a poor response to treatment, a higher frequency of symptoms throughout the neurotic diagnostic spectrum, and a higher tendency to relapse (Tyrer, Seivewright, Ferguson, & Tyrer, 1992).

Moreover, Fava and Bech conceived euthymia as a state characterized by the presence of mood stability rather than well-being (Fava & Bech, 2016). Mood stability is different from both concepts of eudaimonic well-being and hedonic well-being (e.g., Ryff, 1989; Firsch, 2006; Seligman & Csikszentmihalyi, 2000; Rashid & Seligman, 2018). Eudaimonic well-being consists of fulfilling one's potential in a process of self-realization (Ryan & Deci, 2001), whereas hedonic well-being includes subjective well-being, happiness, pain avoidance, and life satisfaction (Ryan & Deci, 2001). Fava and Bech criticized this distinction as unnecessary because each component of well-being is inextricably linked in clinical situations (Fava & Bech, 2016). They also noted that these definitions did not consider the interactions between well-being components and mood fluctuations (Fava & Bech, 2016). On the contrary, mood stability is referred to the idea that it is not possible to suppress stress in all forms, but the goal of each person is to diminish distress and facilitate eustress, that is the positive cognitive response to stress (Lazarus, 1963; 1966; Seyle, 1974). Thus, they advanced the idea that euthymia is a state characterized by the optimal balance between positive and negative cognitions and emotions (Garamoni et al., 1991). This balance protects subjects against relapses and recurrences of affective and neurotic symptoms, more than the absence of illness or the presence of wellness (Fava, 2016a; Fava & Bech, 2016; Guidi, Rafanelli, & Fava, 2019). In fact, also excessively elevated levels of positive emotions can become detrimental and are more connected with mental disorders and impaired functioning (Fava & Bech, 2016).

Starting from these premises, Fava and Bech conceived a comprehensive operational definition of euthymia as a state characterized by mood stability, psychological flexibility, and resilience (Fava & Bech, 2016).

Euthymia was defined as:

a. lack of current mood disturbances that can be subsumed under diagnostic rubrics;

b. patients feel cheerful, calm, active, interested in things and sleep is refreshing or restorative;

c. the patient displays balance and integration of psychic forces (flexibility),unifying outlook on life which guides actions and feelings for shaping future accordingly, and resistance to stress (resilience or frustration-tolerance) (Fava & Bech, 2016).

In order to assess euthymia, Fava and Bech developed the euthymia scale (ES) a ten-item clinimetric self-rating index (Fava & Bech, 2016). The last five items were derived from the 5-item World Health Organization Well-Being Index (WHO-5) (Staehr Johansen, 1998) and reflect the point b of the operational definition reported above. The last five items also include the presence of restorative sleep, that is a homeostatic or allostatic factor enabling the organism to achieve positive mental health (Fava & Bech, 2106). It is indicated by Fava and Bech "among the most significant contributors in the assessment of euthymia" (Fava & Bech, 2106) (p. 4). The first five items incorporate the Jahoda's conceptualization of euthymia (Jahoda, 1958) (i.e., resilience and flexibility) and the presence of mood stability (Seyle, 1974; Garamoni et al., 1991). They pertain to point a and c of the operational definition described above.

Carrozzino, Svicher, Patierno, Berrocal Montiel, and Cosci evaluated the clinimetric proprieties of the ES in two sample: one consisting of type 2 diabetes and one consisting of healthy subjects (Carrozzino et al., 2019). They disclosed a two-dimensional structure of the ES that reflects its development (Carrozzino et al., 2019). The first five items were labelled "Flexibility items", they reflect Jhaoda's flexibility construct and mood stability (Carrozzino et al., 2019). The last five items were labelled "Well-being items", they incorporates the WHO-5 items (Carrozzino et al., 2019). Loevinger's coefficient of homogeneity (H_{ij}) for the total score of the well-being items were acceptable in diabetes outpatients ($H_{ij} = 0.33$), whereas Loevinger's coefficient of homogeneity for the total score of the flexibility items was found acceptable in both samples (healthy subjects: $H_{ij} = 0.33$; diabetes outpatients: $H_{ij} = 0.30$) (Carrozzino et al., 2019).

The assessment of euthymia in medical settings may have important applications and represent how a person experiences the disease process (Fava & Bech, 2106).

There has been recent interest in the relationship between psychological flexibility and chronic pain (McCracken & Morley, 2014). McCracken and Morley conducted a review on psychological approaches to chronic pain management (McCracken & Morley, 2014). They founded that psychological flexibility is one of the most relevant aspects to cope with catastrophizing about pain-related bodily sensations (McCracken & Morley, 2014). Catastrophizing involves the cognitive fusion, an automatic cognitive process where the literal content of thoughts dominates over

other sources of behavior influence (e.g., ''I am worthless, this pain is terrible") (McCracken & Morley, 2014). On the contrary, psychological flexibility was highlighted as a central factor that promotes cognitive defusion (i.e., unbinding cognitive fusion) and present-focused awareness (i.e., allows behavior to influence cognitive contents) (McCracken & Morley, 2014). Thus, psychological flexibility seams to increase patient's momentary thought-behaviors repertoires and develop their personal resources, thus decreasing the severity of irrational beliefs (McCracken & Morley, 2014). In turn, by building psychological flexibility, positive emotions and positive mental states might enhance patient's ability to cope with fearful irrational thoughts, thus reducing pain-related fear and hypervigilance that are mediator of anxiety, disability, psychological distress, and depression (McCracken & Morley, 2014).

A consistent body of data showed that psychological flexibility was found to be a protective factor in the development and exacerbation of psychological distress (Hayes et al., 2006; Levin et al., 2012; Smout et al., 2012). Berrocal Montiel and colleagues investigated the contribution of psychological flexibility to predict adjustment to breast cancer in adult women, finding that higher flexibility at baseline significantly contributed to predict lower anxiety, depression and negative affect at six-month follow-up (Berrocal Montiel et., 2016).

Both psychological flexibility and psychological well-being were found to be protective factor for mental health across different populations (Biglan et al., 2008; Chida & Steptoe, 2008). In this line, many studies in psychosomatic settings provided confirmation of the protective role of well-being, both for mental and physical health (Ruini & Fava, 2012). Wood and Joseph highlighted that an increase in psychological well-being may protect against relapse and recurrence of mood disturbances (Wood & Joseph, 2010). Fava and Sonino outlined that well-being, with the contribution of other factors, can influence the healing process of various diseases and longevity (Fava & Sonino, 2010). Frederickson et al. showed that the presence of high psychological well-being in individuals presented a reduced gene expression of conserved transcriptional response to adversity, thus suggesting a potential protective role of psychological well-being in a number of medical disorders (Frederickson et al., 2015).

3.2 The Concept of Mental Pain

The term mental pain was first identified as "Seelenschmertz" (literally, "soul-pain") (Akhtar, 2000), used by the psychoanalysts for delineating the nature of an internal pain which arises from loss and mourning (Freud, 1954). Freud described the experience of mental pain as a psychological pain caused by the loss of

the object, such as the experience of detachment from attachment figure or loved ones, that evokes analogy to body injury and loss of body part (Freud, 1936). He described mental pain as characterized by a sense of "longing" and "mental helplessness" (Freud, 1936). Mental pain was different from anxiety that results from the anticipating danger caused by the loss of the object (Freud, 1936). It is also different from depression, that evokes "Unlust" (unpleasure) sensations in response to experiences that has already taken place (Freud, 1936; 1954). Mental pain is referred to a "direct experience of mental helplessness related to the feeling of unpleasure which when arises has the specific characteristic of pain" (Freud, 1936) (pp. 171-2). According to this formulation, mental pain arises when psychological pain aroused by the loss of objects and brakes the ego boundaries (i.e., the cognitive/mental representation of the self), leading to a feeling of "ego-rupture" (Freud, 1936). In this vein, cognitive contents of mental pain are frequently associated with physical allusions since the mental representation of ego-rupture and body injuries overlapping (Freud, 1936). Joseph reported the frequency with which physical allusion appears in association with mental pain: "the patient locating it in the lower part of the chest, and yet he knows clearly that he is not describing a physical condition; it is not hypochondriacal or psychosomatic; it is known to be mental. It is experienced as on the border between mental and physical" (Joseph, 1981) (pp. 88-89).

Several attempts have been made to define mental pain over the time. Bakan highlighted the experience of loss as principal component of mental pain, that consequently leads to a disruption in the person's tendency toward maintaining a sense of wholeness and social unity (Bakan, 1968). Similarly, Sandler defined psychological pain as an affective state associated with a sense of discrepancy to ideal and actual perception of self (Sandler, 1962; 1967). Frankl focused on a sense of emotional suffering and emptiness due to the loss of meaning in life (Frankl, 1963). Lastly, Bolger referred to a state of feeling broken encompassing the awareness of loss of self, loss of control, being wounded, and the disconnection from a loved one (Bolger, 1999).

Although these conceptual models have not been validated by empirical study, they expanded on the traditional biomedical model and increased the interest in the experience of mental pain (Gamsa, 1994; Asmundson & Wright, 2004). In this framework, essential characteristics of mental pain were described as sense of feeling broken (ego-rupture), sense of loss or incompleteness of self and awareness of one's own role, as well as sense of being wounded and sense of disconnection from a loved one (Tossani, 2013).

Orbach et al. provided the first definition of mental pain as a distinctive psychological state (Orbach, Mikulincer, Sirota, & Gilboa-Schechtman, 2003). They defined mental pain as "a wide range of subjective experiences characterized as a perception of negative changes in the self and its function that is accompanied by strong neg-

ative feelings" (p. 228). Orbach et al. provided the Orbach and Mikulincer Mental Pain Scale (OMMPS), a standardized self-rating questionnaire for the multidimensional measurement of mental pain (Orbach et al., 2003). The OMMPS encompasses nine factors: irreversibility, loss of control, narcissist wounds, emotional flooding, freezing, self-estrangement, confusion, social distancing, and emptiness (Orbach et al., 2003).

Irreversibility deals with the experience of mental pain as irreversible and perpetual (Orbach et al., 2003). Loss of control contains the experiential components of uncontrollability, unpredictability, helplessness, and ambiguity (Orbach et al., 2003). Narcissist wounds tap the experiential components of hurt-related feelings, such as vulnerability, rejection, and abandonment (Orbach et al. 2003). Emotional flooding includes the experience of intense and overwhelming emotional states (Orbach et al., 2003). Freezing consists of the experience of inability to react to the situation (Orbach et al., 2003). Self-estrangement involves the inability to integrate changes in self-identity (Orbach et al., 2003). Confusion taps difficulties in cognitive function (Orbach et al., 2003). Social distancing consists of approach-avoidance social orientation during the mental pain experience (Orbach et al., 2003). Emptiness encloses the loss of personal meaning produced by the mental pain experience (Orbach et al., 2003).

Mental pain has been also defined in the context of the theories of suicide (Baumeister, 1990; Shneidman, 1993; 1996). Baumeister talked about escape from an aversive state of self-inadequacy (i.e., self-awareness pain) (Baumeister, 1990). The attempt to escape from aversive feelings of emotional pain has been posited as a predictor of higher risk of suicidal behavior and was found to mediates the effects of other psychological variables relevant to suicide (Baumeister, 1990; Shneidman, 1993; 1996).

Shneidman proposed the concept of "psychache" as a contributing factor of suicidal behaviors (Shneidman 1993; 1996). Psychache arises from the frustrated essential psychological needs (e.g., to be loved, to have control, to protect one's self-image, to feel secure) and is expressed through a variety of negative emotions, e.g., shame, guilt, fear, grief, hopelessness, anger (Shneidman, 1998). When the psychache reaches a high intensity, it becomes unbearable and is accompanied by the absence of predictable changes in the future; thus, it may induce patients to suicide (Shneidman, 1993; 1996). The high intensity of psychache can push individuals into a characteristic state that involves feelings of rejection, failure, humiliation, and disorientation concerning the future (Shneidman, 1993; 1996). The intolerable psychache is maintained by frustrated psychological needs and becomes able to overwhelms vital needs (Shneidman, 1993; 1996). Shneidman highlighted that the cognitive contents of internal monologue in the last phases of psychache are interspersed with the word "only" (e.g., "Suicide is the only thing left to do," or "The only way to

commit suicide is by hanging") (Shneidman, 1996).

In the past decades, research on mental pain has yielded a growing body of evidence. Changes in brain functioning were described in association with mental pain and depression (van Heeringen et al., 2010). In depressed patients, results showed that the severity of mental pain and not the severity of depression were associated with changes in cerebral blood flow concerning the areas involved in the processing of emotions (van Heeringen et al., 2010). In this line, strong and persisting emotional input at the prefrontal level was found in depressed individuals become suicidal (van Heeringen et al., 2010). Suicidal behavior risk was found higher when mental pain is intolerable (Shneidman 1998; 1996; van Heeringen et al., 2010) and pain threshold and pain tolerance were found negatively correlated with personal distress in subjects with suicidal behaviors (Orbach et al., 1997; 1996a; 1996b). Indeed, mental pain was found intense in women who suffer from borderline personality (Holm & Severinsson, 2008), numbed in subject exposed to traumatic events (Foa et al., 1992; Monson et al., 2004), and associated to bodily and psychological symptoms which interfere with normal functioning (Nesse, 2005).

In 2016, Giovanni A. Fava located mental pain in the framework of psychosomatic medicine (Fava, 2016a). According to Fava mental pain was conceived as a unitary subjective state of psychological and emotional suffering in the mind (Tossani, 2013; 2014; Fava, 2016a). Mental pain has been differentiated from other emotional suffering associated with traumatic experiences and negative changes such as depression, posttraumatic stress disorder, anxiety (Tossani, 2013). Mental pain has been further differentiated from physical pain perception (i.e., "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"; International Association for the Study of Pain, IASP, 1979) and other types of pain such as nociception, perception of pain, suffering, and pain behaviors (Tossani, 2013). However, the definition of the borderland between mental pain and pain referred to the body is a difficult matter, since pain always involves a psychological component (Tossani, 2013).

Tossani and Fava clearly defined behavioral, cognitive and affective processes involved in mental pain: detaching from a significant other; brokenness of self and psychosocial unity; discrepancy between ideal and actual perception of self; high self-awareness of inadequacy; frustrated psychological needs; negative changes in the self and its function; loss of meaning in life; feelings of guilt, anguish, fear, panic, angst, loneliness, helplessness; experience of being wounded, loss of self, disconnection; critical awareness of one's more negative attributes, sense of incompleteness; torment (Tossani, 2013; Fava, 2016a).

Fava also operationalized the concept of mental pain providing the mental pain questionnaire (MPQ) (Fava, 2016a). He identified 10 clinimetric indicators of a uni-

tary construct: feeling of pain, feeling of heart brokenness, feeling of loss, feeling that pain is everywhere, feeling that pain is always with the individual, inability to understand the cause of pain, sense of emptiness, loss of meaning of life, helplessness, suicidality as an escape from the pain (Fava, 2016a). Svicher and colleagues evaluated the clinimetric properties of the MPQ in a sample of migraine outpatients (Svicher et al., 2109). Both principal component analysis and confirmatory factor analysis confirmed the unidimensional structure of the scale (CFI = 0.94; TLI = 0.91; RMSEA = 0.042). Coefficient of homogeneity (H_{ij}) was found acceptable for the total score (H_{ij} = 0.36) and all the items showed good values of standardized sensitivity parameter, with the exception of item 6 (i.e., inability to understand the cause of pain) (Svicher et al., 2109).

In medical setting, some areas on the research on mental pain could be expanded after decades of neglect (Svicher et al., 2109). Mental pain may provide the clinical threshold that is essential for determining the amount of distress that is worthy of clinical attention, in conjunction with diagnostic criteria (Tossani, 2013). It may offer a better specification of the criterion on 'clinically significant distress' that frequently recurs in DSM nosography (Tossani, 2013). According to the new rationale for well-being interventions introduced by Fava (i.e., the achievement of an optimal balance between psychological well-being and distress), the balance between mental pain and euthymia may deserve attention (Fava, 2016a). Engel, in his formulation of the pain-prone personality, outlined how, in some instances, the expression of psychological distress in terms of cognitive contents related to somatic pain, is protecting the patient from more intense depression and even suicide (Engel, 1959).

3.3 Migraine

Migraine is a common disabling primary headache disorder (International Headache Society, IHS, 2018). According to the International Classification of Headache Disorders 3rd edition migraine is a recurrent headache disorder manifesting in attacks lasting 4-72 hours (IHS, 2018). Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia (IHS, 2018). Migraine encompasses two major subtypes primarily differentiated by headache attack frequency (Buse et al., 2012). Episodic migraine (EM) is characterized by headaches that occur on fewer than 15 days per month (Buse et al., 2012). Chronic migraine (CM) is defined by the presence of migraine with headaches on 15 or more days per month for at least 3 months (Buse et al., 2012).

The World Health Organization in the Global Burden of Disease Study 2015 (GBD, 2015) has classified headache as a major health disorder and it has been rated as the

sixth highest cause of disability worldwide in both males and females under the age of 50 years (Steiner, Stovner, & Vos, 2016). GBD 2016 showed that global age-standardized prevalence for migraine was 14.4% (ranging from 13.8% to 15.0%) overall: 18.9% (ranging from 18.1% to 19.7%) for female, and 9.8% (ranging from 9.4% to 10.2%) for male (GBD, 2016). Worldwide, the age-standardized prevalence of migraine was the highest in Italy and Nepal (Stovnver et al., 2018). Migraine affects women more often than men (gender ratio 3:1), and is most common between the ages of 25 and 55 (Lipton et al., 2003c).

Part of the burden of migraine is produced by the psychiatric (e.g., depression, anxiety, personality disorders) and psychosocial (e.g., impairment of well-being and health-related quality of life) conditions that occur in association with it (Hamelsky & Lipton, 2006).

3.3.1 Psychiatric Comorbidity in Migraine

Investigations concerning the comorbidity of psychiatric disorder have been highly consistent in reporting a high prevalence of psychiatric comorbidities associated with migraine (Radat & Swendesen, 2005; Baskin & Smitherman, 2009; Buse et al., 2013; Minen et al., 2016; McLean & Mercer, 2017). These comorbid conditions compound the negative impact of migraine; their presence is associated with a poorer treatment prognosis, increased disability, and lower satisfaction with medical care (Saunders, Merikangas, Low, Korff, & Kessler, 2008).

The literature on comorbidity between migraine and psychiatric disorders have been considered three basic etiological mechanisms:

a. psychiatric disorders are one of the factors in the multi-causal explanatory models on the development of migraine (Radat & Swendsen, 2005);

b. migraine is a causal factor in the development of psychiatric conditions (e.g., repeated and intense pain leads to anticipatory anxiety or other behavioral and cognitive risk factors for psychiatric syndromes) (Radat & Swendsen, 2005);

c. common shared etiological pathway may explain the co-occurrence of both syndromes without a causal association between them (e.g., a common genetic factor involving neurotransmitter or other abnormalities of the central nervous system) (Radat & Swendsen, 2005).

Depression is one of the most common psychiatric comorbidity in patients with migraine (Peres et al., 2017). The incidence of depression in migraineurs was found highly variable, ranging from 8.6% to 47.9% (Radat & Swendesen, 2005; Zwart et al., 2008; Baskin & Smitherman, 2009). Some studies suggested that depressive disorders are approximately 2.5 times more prevalent among persons with

migraine than in the general population (Baskin & Smitherman, 2009; Zwart et al., 2008; Minen et al., 2016). Patients with CM compared with patients with EM were almost twice as likely to have received a diagnosis of depression (Buse et al., 2012). When CM was compared to the general population the depressive disorders were found to be from 2 to 6 times more prevalent (Zwart et al., 2008; McLean & Mercer, 2017). However, there is no evidence that improved control of depression might help managing the frequency of migraine attacks (Minen et al., 2016). In fact, the relationship between migraine and depression appears to be bidirectional (Breslau et al., 2000), and it was hypothesized that migraine and depression shared causative mechanisms (Minen et al., 2016). The current hypotheses to explain this shared mechanism include serotonergic dysfunction, hormonal influences, and sensitization of the sensory and emotional neural networks (Minen et al., 2016).

Study on the relationship between suicide, suicidal ideation and migraine suggests a modest positive association between migraine and suicidal ideation (Friedman, Gelaye , Bain, & Williams, 2017) and an association between migraine and nonfatal suicidal behavior (Nović, Kõlves, O'Dwyer, De Leo, 2016).

Population studies demonstrated that anxiety disorders (i.e., generalized anxiety disorder, panic disorder, and specific phobias) are more prevalent in subjects with migraine than in the general population (Baskin & Smitherman, 2009). The prevalence of anxiety disorders in migraine sufferers was found ranging from 51% to 58% (Breslau, 1998). Compared to individuals without migraine, migraineurs are at 4-5 times greater risk for generalized anxiety disorder, 3-4 times greater risk for specific phobias, and 3-10 times more likely to suffer from panic disorder (Radat & Swendesen, 2005; Baskin & Smitherman, 2009). As has been found with depression, the prevalence of anxiety is higher among patients with CM than in persons with EM (Baskin & Smitherman, 2009; Buse et al., 2012). Buse et al. showed that a diagnosis of anxiety disorder was significantly more common in subjects with CM than in those with EM (30.2% vs. 18.8 %) (Buse et al., 2010), and a retrospective matched cohort study showed that anxiety disorders were significantly more associated with CM than with EM (Chen, Tang, Ng, & Wang, 2012). Even the relationship between anxiety disorders and migraine appears to be bidirectional (Smitherman, Kolivas, & Bailey, 2012). Anxiety and migraine were found to have a common genetic predisposition associated with a higher frequency of the s allele in a study of the 5HTTLPR polymorphism of the serotonin transporter gene (Gonda et al., 2007). The current hypotheses on the neurobiological mechanism underlying the association between anxiety and migraine include serotonergic dysfunction, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, hormonal influences and psychological factors, such as interoceptive conditioning, pain-related cognition, and avoidance learning and anticipatory anxiety (Minen et al., 2016).

It has also been proposed that both anxiety and depression are risk factors for migraine chronicity (Buse et al., 2013; Lipton, Manack, Serrano, & Buse, 2013). Approximately 2.5% of subjects with EM develop CM each year (Buse et al., 2013). Chronicity was significantly associated with moderate depression (OR = 2.53; 95% CI = 1.06–6.05) (Buse et al., 2013), severe depression (OR = 3.19; 95% CI = 1.26–8.09), and anxiety (OR = 1.53; 95% CI = 1.15–2.04) (Lipton et al., 2013).

Bipolar disorders were found to be associated with migraine, and the association seems to be bidirectional (Buse et al., 2010; 2103). Patients suffering from migraine are three times more likely to suffer from bipolar disorder than the general population, whereas about one-third of patients with bipolar disorder suffer from migraine (Merikangas, Angst, & Isler, 1990; Breslau, Davis, & Andreski, 1991). Among migraine patients, the prevalence of bipolar disorder type II was found higher (54.17%) than that observed in bipolar disorder type I (32.7%) (Fornaro & Stubbs, 2015). Bipolar disorder and migraine were found to share similar features: they are both episodic, worsened by stress, and associated with a family history of affective disorders (Dilsaver et al., 2009). Some data highlighted that migraine and bipolar disorders share common pathophysiology involving the dysfunction of calcium channels (Gordon-Smith et al., 2015).

Post-traumatic stress disorder (PTSD) was found much more prevalent in patients with migraine than in the general population (14-25% vs. 1-12%) (Peterlin et al., 2009; Kessler, 1995). It is even more prevalent in patients with CM compared with patients with EM (43% vs. 9%) (Peterlin et al., 2009; Kessler, 1995). Current hypotheses on the neurobiological mechanism underlying the association between PTSD and migraine include serotonergic, autonomic nervous system, and HPA axis dysfunction (Juang & Yang, 2014).

Borderline personality disorder reported a prevalence of about 2% in the general population and appeared to be disproportionately prevalent in the migraine patient population (Rothrock et al., 2007). However, data on the association between borderline personality and migraine appeared unclear (Minen et al., 2016). Only studies conducted on headache clinical populations are available showing that borderline personality disorder is associated with more pervasive headache and greater migraine-related disability (Rothrock et al., 2007).

3.3.2 Psychosocial Impairment in Migraine

Stress is the most prevalent migraine trigger (Dodick, 2009). Patients with migraine tend to suffer from high levels of stress, especially those with CM (Dodick, 2009). Exposure to chronic repeated stress (including repeated migraines) leads to allostatic dysfunction, manifested as both structural and functional damage (Bor-

sook, Maleki, Becerra, & McEwen, 2012). These negative changes impact pain processing, induce central sensitivity, and might affect the pain experience in patients with migraine (Borsook et al., 2012). Functional MRI showed migraine patients have more activation in the perigenual cortex than patients without migraine, which was found to be one of the brain areas associated with allostatic dysfunction (Tessitore et al., 2011). Exposure to chronic stress in both early life and adulthood was found to decrease the expression of glucocorticoid receptors (GR) upregulate the expression of the cochaperone gene (FKBP5) which restrains GR activity by limiting the translocation of the receptor complex to the nucleus and alter transcriptional activity (Cattaneo & Riva, 2016). In turn, chronic stress was found to impact gene function, response to future stressors, and susceptibility to further stressors, migraine, and psychiatric disorders (Cattaneo & Riva, 2016).

Restorative sleep is a homeostatic or allostatic factor enabling the organism to achieve psychological well-being (Fava & Bech, 2016). Migraine patients showed a high prevalence of severe sleep disturbances than the general population (OR = 5.4; 95% CI = 2.0–14.5) (Rains & Poceta, 2006; Ødegård et al., 2010). More than a third of migraine subjects suffer from chronic short sleep (i.e., ≤6 h per night) which is associated with more severe headaches (Kelman & Rains, 2005). The relationship between migraines and sleep was found to be bidirectional (Dosi, Figura, Ferri, & Bruni, 2015): sleep disturbances are known triggers and risk factors for migraines, and on the opposite, migraines interfere with the quality of sleep of patients (Dosi et al., 2015).

Migraine patients were found more alexithymic than controls (Muftuoglu et al., 2004; Yalug et al., 2010; Bablan et al., 2012). However, the percentage of alexithymia in migraineurs was found highly variable ranging from 70% to 12.9% (Muftuoglu et al., 2004; Bablan et al., 2012). Yalug et al. showed that CM and EM did not differ on alexithymic features (Yalug et al., 2010)

Irritability was found to be a migraine trigger, showing a significant increase in migraine risk in individuals with migraine relative to those without migraine: OR = 3.8; 95% CI = 1.9–7.8 if experienced some days, OR = 7.5; 95%; CI = 2.7–20.7 more than half the days, and OR = 22.0; 95% CI = 5.7–84.9 when experienced nearly every day (Peres et al., 2017).

Somatic symptoms in headache patients are less well studied than other psychological symptoms (Tietjen et al., 2007). Comorbidity of functional somatic symptoms with migraine was found more common in CM than EM (Maizels & Burchette, 2004). Most frequent specific symptoms were fatigue (73%), sleep difficulty (60%), and nausea/indigestion (55%) (Maizels & Burchette, 2004). In a sample of migraine women, Tietjen et al. found that women with CM were three times more likely than those with EM to report a high degree of somatic symptom severity (Tietjen et

al., 2007). They highlighted as the most prevalent somatic symptoms: constipation, loose bowels, or diarrhea (OR = 1.6; 95% CI = 1.2–2.2); nausea, gas, or indigestion (OR = 1.9; 95%; CI = 1.4–2.5); feeling tired or having low energy (OR = 2.5; 95%; CI = 1.9–3.4). (Tietjen et al., 2007).

Several studies documented the persistently low levels of psychological well-being in migraine sufferers (Shields & Wheatley Price, 2005). Migraine has a profound effect on well-being and general functioning, not only during the acute attack, but also in terms of work performance, family, and social relationships (Wessman, Terwindt, Kaunisto, Palotie, & Ophoff, 2007). Migraineurs had a lower quality of life than the general population (Lipton et al., 2003a; Lipton et al., 2003c; Hamelsky, Lipton, & Stewart, 2005). A population-based study run in the UK reported a lower quality of life in patients with a moderate or severe migraine (Hamelsky et al., 2005). The greatest differences were found on role–physical (i.e., the impact of health on work and related activities), bodily pain (i.e., severity of bodily pain in the past month and its impact on work or chores), social functioning (i.e., impact of health on participation in social activities.), and role–emotional (the impact of emotional unhealth on work and other activities) scales of the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36). The lower quality of life remains after adjustments for socioeconomic status and depression (Hamelsky et al., 2005).

Family functioning was found to be negatively affected by migraine both from the perspective of those with migraine and from the perspective of their relatives (Lipton et al., 2003a). Lipton et al., suggested that migraine could disrupt family life (Lipton et al., 2003a). Among patients with migraine living with a household partner, 85% reported substantial reductions in their ability to do household work and 45% missed family, social, and leisure activities (Lipton et al., 2003a). People with migraine frequently cancel family or social activities (Rueveni, 1992; Smith, 1998), thereby generating guilt toward their spouses and children (Basolo-Kunzer, 1991). Partners of people with migraine reported decreased work performance and dissatisfaction with their work demands, responsibilities and duties, compared with healthy controls (Smith, 1998). The frequency and quality of sexual relationships were found decreased (Smith, 1998). Migraine patients and their spouses, compared with couples without migraine had greater problems with cohesion (Lipton et al., 2003a).

3.4 The PAINMIG Study: Aims

Despite an extensive body of research has been conducted on the link between migraine and comorbid psychiatric disorders (e.g., Baskin & Smitherman, 2009; Buse et al., 2013; Minen et al., 2016), no studies have examined the relationship

between mental pain and migraine, yet. The mental pain questionnaire (MPQ) has been recently validated in a sample of migraine outpatients (Svicher et al., 2019). Mental pain merits to be studied among migraineurs since there is evidence on the relationship between mental pain, pain threshold, pain tolerance, and suicidal behaviors (Orbach et al., 1997; 1996a; 1996b) as well as mental pain is a useful index determining the amount of distress that is worthy of clinical attention (Tossani, 2013; 2014).

A large variety of studies investigated the link between migraine, well-being, or quality of life (e.g., Lipton et al., 2003a; Lipton et al., 2003c; Hamelsky et al., 2005). However, migraine patients have never been assessed according to the new concept of euthymia, yet. Recently, the Euthymia Scale was developed (Fava et al., 2016) and validated (Carrozzino et al., 2019). Euthymia deserves attention among migraine sufferers since aspects of psychological flexibility were found associated with positive functioning and wellbeing in people with headache disorders (Almarzooqi, Chilcot, & McCracken, 2017; Foote et al., 2015). Interventions emphasizing psychological flexibility (e.g., Acceptance and Commitment Therapy) yielded significant reductions in the maladaptive response of avoidance of headache (Almarzooqi et al., 2017; Foote et al., 2015). Moreover, an RCT protocol testing the efficacy of the WBT in migraine outpatient was recently developed (Mansueto et al., 2019).

Psychosocial variables in migraine patients, such as stress, sleep disturbances, alexithymia, somatic symptoms, and family functioning have been analyzed elsewhere (e.g., Muftuoglu et al., 2004; Hamelsky et al., 2005; Shields & Wheatley Price, 2005; Tietjen et al., 2007; Ødegård et al., 2010; Dodick, 2009). There has not, however, data on the relationship between DCPR-R psychosocial syndrome and migraine. Psychosocial syndromes deserve attention among migraine sufferers since their prevalence was found high in other medical settings (e.g., cardiology, gastroenterology, dermatology) (Porcelli & Rafanelli, 2010). The Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview (DCPR-R-SSI; Fava, Cosci, & Sonino, 2017) has been recently validated in a sample of migraine outpatients (Cosci et al., 2019). Moreover, a huge body of data showed that DCPR syndromes have a significant impact on prognostic factors, such as individual vulnerability, therapeutic response to treatment, and outcome to a given illness episode (Fava, Belaise, & Sonino, 2010; Fava, Cosci, & Sonino, 2017).

The main purposes of the present study, labeled "PAINMIG: cohort study for the evaluation of mental pain in migraine patients" are:

a. assessing and comparing the levels of mental pain, euthymia, and DCPR-R psychosocial syndromes among CM, EM, and healthy subject;

b. assessing and comparing mental disorders, body pain, levels of depressive

symptoms, disability due to migraine, and biopsychosocial functioning among CM, EM, and healthy subject;

c. calculating the risk and protective factors for both EM and CM concerning psychosomatic, psychosocial, and psychiatric variables;

d. providing comparisons among migraine subjects with and without mental pain concerning psychosomatic, psychosocial, and psychiatric variables;

e. calculating the risk and protective factors for mental pain in migraine subjects concerning psychosomatic, psychosocial, and psychiatric variables.

4 Methods

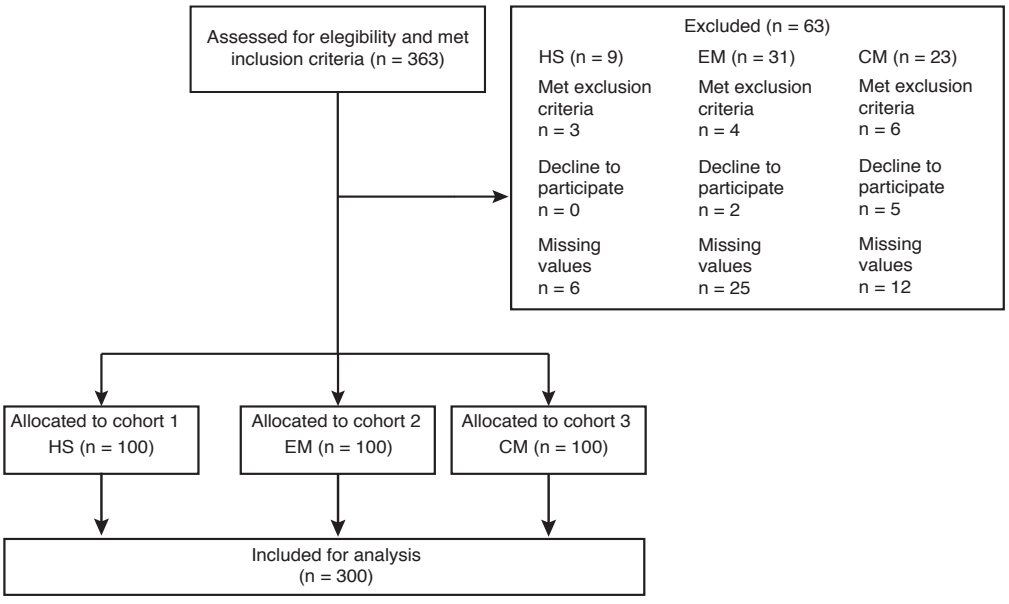
4.1 Study Design

The PAINMIG study is a cohort study with a cross-sectional analysis of the variables of interest age-matched and gender-matched. It was designed to study psychosocial and psychological variables among chronic migraine subjects, episodic migraine subjects, and healthy controls, as well as between migraine subjects with and without mental pain.

4.2 Participants

Migraine patients were consequently enrolled at the Headache and Clinical Pharmacology Center of the Academic-Hospital Careggi of Florence (Tuscany, Italy). One hundred chronic migraine subjects (CM) and 100 episodic migraine subjects (EM) were assigned to two different groups. One hundred healthy volunteers (HS) were enrolled from the general population of Tuscany (Italy), and assigned to a third group. The three groups were matched for age (± 2 years) and sex (ratio 2:1). The period of recruitment was from November 2016 to April 2019. Figure 6 shows the CONSORT subject flow diagram of the study encompassing the number of subjects screened and enrolled.

Figure 6. CONSORT diagram of the PAINMIG study



HS: Healthy subjects; EM: Episodic Migraine subjects; CM: Chronic Migraine subjects

4.2.1 Exclusion and Inclusion Criteria

EM Subjects had to meet the following inclusion criteria: (1) a clinical diagnosis of episodic migraine according to the International Classification of Headache Disorders, 3rd edition (beta version) (IHS, 2013); (2) age from 18 to 64 years. The exclusion criteria applied were: (1) cognitive deficits or other intelligence problems affecting the ability of reading and understanding Italian language; (2) mother tongue other than Italian.
CM subjects had to meet the following inclusion criteria: (1) a clinical diagnosis of chronic migraine according to the International Classification of Headache Disorders, 3rd edition (beta version) (IHS, 2013); (2) age from 18 to 64 years. The exclusion criteria applied were: (1) cognitive deficits or other intelligence problems affecting the ability of reading and understanding Italian language; (2) mother tongue other than Italian.
The inclusion criteria applied to the HS sample were: (1) age ranging from 18 to 64 years.
The exclusion criteria were: (1) cognitive deficits or other intelligence problems affecting the ability of reading and understanding Italian language; (2) mother tongue other than Italian; (3) current or lifetime diagnosis of migraine.
Participation was voluntary. Respondents had to provide a signed written informed consent according to the Helsinki Declaration including a privacy protection disclaimer. The research study was approved by the Institutional Review Board of the Academic-Hospital Careggi of Florence (Florence, Italy).

4.3 Procedure

Migraine patients were assessed by an expert physician and diagnosed with chronic migraine (≥ 15 days of migraine/month) or episodic migraine (< 15 days of migraine/month) according to the International Classification of Headache Disorders, 3rd edition (beta version) (International Headache Society, 2013). Thereafter, they were invited to complete a clinical interview conducted by trained clinical psychologists. Healthy subjects were recruited through advertisements posted on social networking service (i.e., Facebook, Inc.) and flyers posted in local businesses, academic places, and community bulletin boards. Those who agreed to take part in the study and met the inclusion criteria were invited to complete a clinical interview conducted by trained clinical psychologists.

4.4 Assessment

The clinical interview for both migraine subjects and healthy subjects included a structured interview investigating socio-demographic and anamnestic information (Guidi et al., 2015).
Socio-demographic variables includes:

a. age;
b. gender;
c. marital status (i.e., unmarried, married, cohabitant, separated divorced, and widow/er);
d. educational level (i.e., primary school, secondary school, high school, bachelor or master degree; Ph.D. or post-graduate educational level);
e. employment (i.e., worker or subordinate; employee; self-employed; freelance; manager/executive; retired; student; unemployed).

Anamnestic variables encompassed:

a. past hospitalizations;
b. food/drug allergies;
c. lifetime history of psychiatric disorders;
d. daily alcohol consumption;
e. daily cigarettes consumption;
f. substance abuse;
g. daily coffee consumption;
h. lifetime history of psychotherapeutic treatment;
i. current psychotherapeutic treatment.

Thereafter, subjects were evaluated by trained clinical psychologists who run: two self-rating indexes assessing migraine and disability related to migraine (i.e., the ID Migraine, and the Migraine Disability Assessment Questionnaire) (Lipton et al., 2003b; Stewart et al., 1999); a self-rating scale for the assessment of pain (the Brief Pain Inventory) (Cleeland & Ryan, 1994); three semi-structured interview for the assessment of psychosocial syndromes, mental disorders, and depressive symptoms (i.e., the Diagnostic Criteria for Psychosomatic Research-Revised, the Structured Clinical Interview for DSM-5 disorders, and the Clinical Interview for Depression) (Fava, Cosci, & Sonino, 2017; First, Williams, Karg, & Spitzer, 2016; Paykel, 1985); a self-rating scale for the assessment of mental pain (i.e., the Mental Pain Questionnaire) (Fava, 2016a); a self-rating scale for the assessment of the euthymia (i.e., the Euthymia Scale) (Fava & Bech, 2016); and a self-rating scale assessing psychosocial functioning (i.e., the PsychoSocial Index) (Sonino & Fava, 1998).

4.5 Instruments

4.5.1 The ID Migraine

The ID Migraine (Lipton et al., 2003b) is a four-item screening tool for migraine. The subjects indicate the extent to which they have experienced migraine symptoms or disability during the last three months on a dichotomous scale (i.e., yes/no) (Lipton et al., 2003b). The first question investigates the presence of migraine attacks in the last three months and the other three items consist of questions on disability, nausea, and photophobia (Lipton et al., 2003b). The ID Migraine was found to be a valid and reliable screening instrument tool for migraine headaches in the primary care setting (Lipton et al., 2003b). ID migraine showed a sensitivity of 0.81 (95% CI = 0.77–0.85) and a specificity of 0.75 (95% CI = 0.64–0.84) relative to an IHS-based migraine diagnosis assigned by a headache specialist (Lipton et al., 2003b). The ID Migraine also showed good test-retest reliability with a kappa of 0.68 (Lipton et al., 2003b). The Italian version of the ID Migraine showed excellent psychometric proprieties with high sensitivity (0.95), specificity (0.72), positive predictive value (0.88), and good accuracy (Area Under the Receiver Operating Characteristic curve; AUC = 0.87) (Brighina et al., 2008).

4.5.2 The Migraine Disability Assessment Questionnaire

The Migraine Disability Assessment Questionnaire (MIDAS) (Stewart et al., 1999) is a five-item disability-related self-report scale covering the previous 3-month (Stewart et al., 1999). It allows patients to score the number of lost days due to the migraine in three domains: school or paid work; household work; family, social, or leisure activities (Stewart et al., 1999).

Item 1 and 2 investigate paid work, enquiring as to the number of days of work off, and the number of days where productivity was reduced by half or more, respectively (Stewart et al., 1999). Item 3 and 4 investigate the same indicators (i.e., number of days off and number of days with as at least 50% reduced productivity) about household works (Stewart et al., 1999). Item 5 concerns about missed days of recreational, social, and family activities (Stewart et al., 1999).

The MIDAS score is obtained via the sum of the scores (i.e., the number of days affected) of the five items. The scores reflect four grades of disability: grade I (score 0-5), minimal or infrequent disability; grade II (score 6-10), mild or infrequent disability; grade III (score 11-20), moderate disability; grade IV (score 21 or more), severe disability. CM was found to be more likely in MIDAS grade IV than EM (CM = 64.3% versus EM = 43.2%; p = 0.001) reflecting the great likelihood of severe

disability in this group (Bigal et al., 2003).
Cronbach's alpha of the scale was found ranging from 0.73 to 0.76 (Stewart et al., 1999). The test-retest Spearman correlation was found good ranging from 0.54 to 0.82 (Stewart et al., 1999). The MIDAS was also tested in comparison to a headache diary (Stewart et al., 2000). The spearman correlation between the MIDAS summary score and the diary score was found to be 0.63 (Stewart et al., 2000). The Italian version of MIDAS has shown psychometric properties consistent with the original version: good internal consistency (Cronbach's alpha = 0.70) and good test-retest reliability (Spearman's rho correlation = 0.77) (D'Amico et al., 2001).

4.5.3 The Brief Pain Inventory

The Brief Pain Inventory (BPI) (Cleeland & Ryan, 1994) is a self-administered 9-item questionnaire that consists of questions on pain intensity and pain-related interference that occurred in the last 24 hours. It also queries the patients about pain relief, pain quality, and pain location on the body areas (Cleeland & Ryan, 1994). The first question is a screening item assessing the pain quality (i.e., pain different from minor headaches, sprains, and toothaches) on a yes/no answer (Cleeland & Ryan, 1994). The second question assesses the area/areas where subjects feel pain via a simple graphical representation of the human body (Cleeland & Ryan, 1994). The item from 3 to 6 ask patients to rate their pain at the time of responding to the questionnaire (pain now) and pain at its worst, least, and average for the last 24 hours (Cleeland & Ryan, 1994). Responses are rated on four 0 to 10 scales (Cleeland & Ryan, 1994). Each scale is presented as a horizontal row of equidistant numbers from 0 to 10 and is bounded by the words "no pain" at the 0 ends and "pain as bad as you can imagine" at the others (Cleeland & Ryan, 1994). Using the same type of 0 to 10 scales, item 9 asks patients to rate separately how their pain interferes with several life domains (Cleeland & Ryan, 1994). It encompasses seven points: (a) general activity; (b) mood; (c) walking; (d) work; (e) relations with others; (f) sleep; (g) enjoyment of life (Cleeland & Ryan, 1994). The BPI was designed to capture three dimensions of pain: severity and activity as well as affect (emotions) interference (Cleeland & Ryan, 1994).
The three-factor model (i.e., pain severity, activity interference, and affect interference) was found statistically superior (RMSEA = 0.075; CFI = 0.953) when compared with the one-factor (RMSEA = 0.081; CFI = 0.750) or the two-factor model (RMSEA = 0.081; CFI = 0.941) (Atkinson et al., 2011). The Italian version has shown similar psychometric properties to the English one, showing a three-factor structure and Cronbach's alphas ranging from 0.71 (pain severity) to 0.81 (activity interference) (Caraceni et al., 1996).

4.5.4 The Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview

The Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview (DCPR-R-SSI; Fava, Cosci, & Sonino, 2017) is a semi-structured interview based on the DCPR-R. It has four diagnostic modules (i.e., stress, illness behaviour, psychological, manifestation, personality) to formulate the diagnoses of: allostatic overload, health anxiety, disease phobia, hypochondriasis, thanatophobia, illness denial, persistent somatization, alexithymia, conversion symptoms, anniversary reaction, somatic symptoms secondary to a psychiatric disorder, demoralization, demoralization with hopelessness, irritable mood, type-a behavior, alexithymia (Fava, Cosci, & Sonino, 2017). The interview focuses on the last 12 or 6 months and consists of 79 yes/no items (Fava, Cosci, & Sonino, 2017).
The semi-structured interview for DCPR showed excellent psychometric properties in terms of construct validity, predictive validity (Porcelli & Sonino, 2007; Tomba & Offidani, 2012; Galeazzi et al., 2004), and inter-rater agreement ranging from k = 0.69 (irritable mood) to k = 0.97 (disease phobia) (Galeazzi et al., 2004). The Italian version of the semi-structured interview for DCPR-R has been investigated in a sample of migraine outpatients showing satisfactory clinimetric proprieties (Cosci et al., 2019). It showed good incremental validity over the diagnoses of SCID-5 yielding a significant increase in the prediction of psychosocial dimensions (Cosci et al., 2019). Incremental validity was found to range from $R^2 = 0.24$ ($\Delta R^2 = 0.06$; $p \leq 0.001$) for PsychoSocial Index Quality of Life to $R^2 = 0.24$ ($\Delta R^2 = 0.07$; $p \leq 0.01$) for PSI Distress. Discriminant validity was found to differentiate between subjects with and those without a DCPR-R diagnosis in terms of PSI Well-being ($p = 0.001$), PSI Stress ($p \leq 0.001$), and PSI Psychological Distress ($p = 0.008$) (Cosci et al., 2019).

4.5.5 The Structured Clinical Interview for DSM-5 – Clinician Version

The Structured Clinical Interview for DSM-5-Clinician Version (SCID-5-CV; First, Williams, Karg, & Spitzer, 2016) is a semi-structured interview assessing DSM-5 disorders. It has five diagnostic modules (Glasofer, Brown, & Riegel, 2015) and five tree-structure modules which allow evaluating diagnostic hypotheses (Spitzer, Williams, Gibbon, & First, 1992). SCID-5 allows to evaluate mood schizophrenia spectrum and other psychotic disorder, bipolar and related disorders, depressive disorders, substance use disorders, panic disorder, agoraphobia, social anxiety disorder, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, attention-deficit/hyperactivity disorder, adjustment disorder (First, Williams, Karg, & Spitzer, 2016).

The SCID represents the gold standard for assessing mental disorders. It showed high-reliability scores (kappa values 0.60 - 1.00) and a good test-retest validity (Glasofer, Brown, & Riegel, 2015). The psychometric properties of the Italian version are consistent with the English one (First, Williams, Karg, & Spitzer, 2017).

4.5.6 The Clinical Interview for Depression – Shorter form

The Clinical Interview for Depression – shorter form (CID; Paykel, 1985; Guidi, Fava, Bech, & Paykel, 2011) is a 20-item semi-structured interview assessing a wide range of symptoms related to depressive syndromes, including both psychic and somatic anxiety (Paykel, 1985). It is based on an expanded version of the Hamilton Rating Scale for Depression (Hamilton, 1960) and it is rated on a 7-point Likert scale with a specification of each anchor point based on severity, frequency, and/or quality of symptoms (Guidi et al., 2011). The CID investigates the last week (Guidi et al., 2011). The most common type of item requires a retrospective rating of the condition based on the patient's account (Guidi et al., 2011). For most of these, symptoms are averaged over time, while for a few, such as suicidal tendencies, a rating is made of the maximal behavior shown over the week (Guidi et al., 2011). The second major type of item is rated on observable behavior or verbal interaction manifested (Guidi et al., 2011). The CID shorter form allows to assess: feelings of depressed mood; distinct quality of depression; diurnal variation, symptoms worse in the morning; diurnal variation, symptoms worse in latter half of day; reactivity to social environment; guilt, lowered self-esteem, and worthlessness; pessimism and hopelessness; suicidal tendencies; work and interests; energy and fatigue; anxiety psychic, generalized; panic attacks; phobic anxiety; anxiety somatic; anorexia; increased appetite; weight loss; irritability; initial insomnia; delayed insomnia; agitation; depressed appearance (Guidi et al., 2011). Scores for anxiety and depression can be calculated as well as individual items that are suitable for use as separate measures (Guidi et al., 2011). The CID showed excellent psychometric and clinimetric properties in terms of inter-rater reliability (Cohen k ranging from 0.81 to 0.82; agreement rates ranging from 95% to 97%), discriminant validity, sensitivity to changes with treatment, test-retest reliability (depression r = 0.58; anxiety r = 0.59), concurrent and divergent validity (Paykel, 1985; Guidi et al., 2011). Moreover, the scale was found consistent with a two-factor structure (Paykel, 1985; Rassaby & Paykel, 1979). The Italian version showed clinimetric and psychometric properties consistent with the English version (Grandi et al., 1990; Fava, Savron, Zielezny, Grandi, Rafanelli, & Conti, 1997).

4.5.7 The Mental Pain Questionnaire

The Mental Pain Questionnaire (MPQ; Fava, 2016a; Fava, 2017) is a 10-item self-report questionnaire in which respondents refer the extent to which they are suffering from mental pain in the last week. It includes statements on sense of emptiness, loss of meaning and suffering that mental pain entails (e.g., my pain is everywhere, my life makes no sense, the only way to interrupt pain is to die) (Fava, 2016a) which are formulated in a dichotomous response format (e.g., yes/no, true/false) (Fava, 2016a). The total score of the euthymia scale ranges from 0 to 10 and higher scores indicate a higher level of mental pain. Svicher et al. evaluated the clinimetric proprieties of the MPQ in a sample of Italian migraine outpatients via an Item Response Theory Analysis (Svicher et al., 2019). MPQ showed a unidimensional factor structure with all the items loading onto one factor with excellent values ranging between 0.50 and 0.81 (Svicher et al., 2019). CFA of the one-component model was found to have adequate fit to the data (CFI = 0.94; TLI = 0.91; RMSEA = 0.042) (Svicher et al., 2019). All the items showed standardized sensitivity parameter values > 1.00 indicating good ability to distinguish the presence of mental pain with the exception of item 6 (i.e., "I cannot understand why I feel this pain"), which showed a low standardized sensitivity parameter (Svicher et al., 2019). Homogeneity of the item ranging from Loevinger coefficient of 0.49 to 0.23 (Svicher et al., 2019). The homogeneity of the total score was 0.36 (Svicher et al., 2019).
The overall reliability of the scale was acceptable with a Cronbach's alpha of 0.77 and a Sijtsma and Molenaar Rho of 0.76 (Svicher et al., 2019). An MPQ score of at least 2 was found to measure psychological distress and stress with acceptable sensitivity and specificity compared to the PSI scores showing AUC (95% CI) ranging from 0.739 (0.67 – 0.79) to 0.636 (0.56 – 0.70) (Svicher et al., 2019). A score of 3 or more was found to provide a measure of mental pain clinically relevant whit acceptable sensitivity and specificity with the CID scores showing AUC (95% CI) ranging from 0.859 to 0.733 (Svicher et al., 2019).

4.5.8 The Eutymia Scale

The Euthymia Scale (ES) is a 10-item self-administered scale (Fava & Bech, 2016) assessing the following psychological dimensions: (a) lack of mood disturbances; (b) cheerfulness, relaxation, interest in things, and refreshing or restorative sleep; (c) psychological flexibility and resilience. Each item in the scale is scored dichotomously as 1 (True) or 0 (False) (Fava & Bech, 2016). The last 5 items in the Euthymia Scale covered a state of psychological well-being (scores ranging from 0 to 5), while the first 5 items assess psychological flexibility (scores ranging from 0 to 5)

(Carrozzino et al., 2019). The ES displayed good clinimetric properties (Carrozzino et al., 2019). In diabetes outpatients, incremental validity of the ES on the WHO-5 was found good, providing an incremental contribution to the prediction of the PWB Autonomy subscale ($\Delta R^2 = 0.12$; $p < 0.001$), PWB Environmental Mastery ($\Delta R^2 = 0.10$; $p < 0.001$), PWB Purpose in Life ($\Delta R^2 = 0.13$; $p < 0.001$), and Self-Acceptance ($\Delta R^2 = 0.09$; $p < 0.001$) (Carrozzino et al., 2019). A similar result was obtained in the group of healthy controls (Carrozzino et al., 2019). The 5-item of psychological flexibility obtained a statistically acceptable level of scalability with a Loevinger's coefficient (H_{ij}) of 0.33 in diabetes outpatients, just below the level of acceptability in the sample of healthy controls ($H_{ij} = 0.28$) (Carrozzino et al., 2019). The 5-item of well-being showed a level of scalability that was found acceptable both in the sample of diabetes outpatients ($H_{ij} = 0.34$), and in the group of healthy controls ($H_{ij} = 0.30$) (Carrozzino et al., 2019).

4.5.9 The Psychosocial Index – Self-rating Scores

The Psychosocial Index (PSI; Sonino & Fava, 1998) is a questionnaire assessing distress, stress, well-being, and quality of life to be used in clinical settings. The self-report part, which was used for the present research, consists of 55 items derived from previous validated instruments: Screening List for Psychosocial Problems (SLP) (Kellner, 1991), Stress Profile (Wheatley, 1990), Psychological Well-being Scales (Ryff, 1989), and a simple direct question on Quality of Life following Gill and Feinstein's recommendations (Gill & Feinstein, 1994). Items are rated on four subscales: Stress, Psychosocial distress, Illness behaviour, Well-being, Quality of life (Piolanti et al., 2016). Most of the items are rated on a yes/no answer while some are rated on a 4 point Likert scale (from "not at all" to "a great deal"); the item on quality of life can be answered on the basis of five possible choices (from "awful" to "excellent") (Piolanti et al., 2016). The stress subscale contains an integration of both perceived and objective stress, life events, and chronic stress (Piolanti et al., 2016). It consists of 17 dichotomous questions with a total score ranging from 0 to 17 (Piolanti et al., 2016). Well-being subscale covers different areas of well-being, i.e., positive relations with others, environmental mastery, and autonomy (Piolanti et al., 2016). They are six items on a dichotomous format and the score ranging from 0 to 6 (Piolanti et al., 2016). The psychological distress subscale consists of a checklist of five symptoms on a 4 point Likert scale addressing sleep disturbances, somatization, anxiety, depression, and irritability (Piolanti et al., 2016). The total score may range from 0 to 45. Abnormal illness behavior subscale allows the assessment of hypochondriacal beliefs and bodily preoccupations symptoms trough tree item on a 4 point Likert scale (Piolanti et al., 2016). The total score may range from 0 to 9 (Piolanti et al., 2016). The PSI self-rating scores were applied in a large variety of

medical patients such as hypertensive subjects with primary aldosteronism, subjects with medically unexplained syncope, patients who underwent coronary artery by-pass, and breast cancer survivors (Piolanti et al., 2016). The Italian version has shown similar performances to the English one (i.e., intraclass correlation coefficients ranging from 0.94 to 0.80; excellent inter-rater concordance) (Sonino & Fava, 1998).

4.6 Statistical Analysis

4.6.1 Groups Analyzed

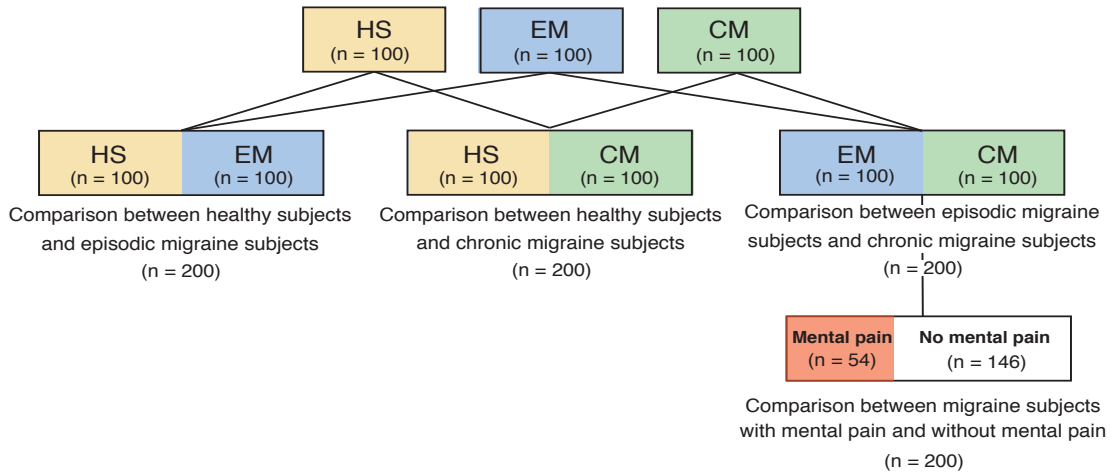
Figure 7 shows the matching procedure ran for the group's comparisons. Three groups were selected for the statistical analyses:

a. group for the comparison of healthy subjects and episodic migraine subjects (n = 200) composed of 100 subjects with a diagnosis of EM and 100 healthy volunteers (Figure 7);

b. group for the comparison of healthy subjects and chronic migraine subjects (n = 200) composed of 100 subjects with a diagnosis of CM and 100 healthy volunteers (Figure 7);

c. group for the comparison of episodic migraine subjects and chronic migraine subjects (n = 200) composed of 100 subjects with a diagnosis of EM and 100 subjects with a diagnosis of CM; the groups of EM and CM subjects was subsequently analyzed comparing subjects with and without mental pain according to the MPQ cut of score of ≥ 3; 54 migraine subjects showed mental pain, and 146 migraine subjects showed no mental pain (Figure 7).

Figure 7. Groups selected for data analysis: Matching procedures



HS: healthy subjects; EM: episodic migraine subjects; CM: chronic migraine subjects; Mental pain: migraine subjects with clinically relevant mental pain; No mental pain: migraine subjects without clinically relevant mental pain

4.6.2 Comparison between Groups

Comparison between groups of subjects were conducted via chi-squared test for discrete variables (e.g., sociodemographic variable, anamnestic variables, SCID-5 diagnoses, DCPR-R-ISS diagnoses, ID Migraine, MIDAS disability grades), via the Kruskal–Wallis test for ordinal data (i.e., number of SCID-5 diagnoses, number of DCPR-R diagnoses), and via the Mann–Whitney *U* test for continuous data since they were not normally distributed (i.e., age, BPI scores, CID scores, MPQ scores, ES scores, PSI scores). A p-value ≤ 0.05 was considered statistically significant (two-tailed). The Statistical Package for the Social Sciences version 21.0.0 (SPSS, Inc.) was used.

4.6.3 Univariate and Multivariate Logistic Regression Analyses

Univariate logistic regression analyses were run using each psychiatric and psychosocial rating scale score as the independent variable (i.e., SCID 5, DCPR-R-ISS, CID, ES, MPQ, ES, PSI). The worst clinical condition was set as dependent variables as follow:

a. Comparison between healthy subjects and episodic migraine subjects (n = 200): HS = 0, EM =1;

b. comparison between healthy subjects and chronic migraine subjects (n = 200): HS = 0, CM =1;

c. comparison between episodic migraine subjects and chronic migraine subjects (n = 200): EM = 0, CM = 1;

d. comparison between migraine subjects with clinically relevant mental pain and without clinically relevant mental pain (n = 200): No mental pain = 0, Mental pain = 1.

The following adjustment variables were selected.

a. In the comparison between healthy subjects and episodic migraine subjects were selected food/drug allergies, daily use of pharmacological treatments, daily alcohol consumption, and daily smoking since they showed a statistically significant difference between EM and HS.

b. In the comparison between healthy subjects and chronic migraine subjects were selected lifetime history of psychiatric disorders, daily use of pharmacological treatments, daily use of alcoholic beverages, daily smoking since they showed a statistically significant difference between CM and HS.

c. In the comparison between episodic migraine subjects and chronic migraine

subjects were selected daily use of pharmacological treatments, lifetime history of psychiatric disorders, and lifetime psychotherapy treatment since they showed a statistically significant difference between EM and CM.

d. In comparison between migraine subjects with and without mental pain were selected age and sex since they were not age and gender-matched as well as educational level, migraine severity, lifetime psychiatric disorders, daily smoking, and current psychotherapy treatment since they showed a statistically significant difference between the two groups.

The calculation of the risk and protective factors were provided via the Odds Ratio (OR) values (Hosmer & Lemeshow, 2000). OR ≥ 1 indicates a risk factor for the worst clinical condition; OR < 1 indicates a protective factor for the worst clinical condition (Hosmer & Lemeshow, 2000).

Thereafter, psychiatric and psychosocial predictors founded with OR ≥ 1 at the univariate analyses, were included in multivariate logistic regression analysis to calculate multivariate models of risk factors. Similarly, psychiatric and psychosocial predictors founded with OR < 1 at the univariate analyses were included in multivariate logistic regression analysis to calculate multivariate models of protective factors.

For fine-scale analyses an inspection of skewness and kurtosis was run for each variable analyzed via logistic regressions; values in the range of ± 3 were considered adequate (Tabachnick & Fidell, 2012). To control the heteroscedasticity due to the non-normal variables, the calculation of OR was implemented via robust variance estimation (Carrol & Pederson, 1993). The JASP 0.10.2 interface (University of Amsterdam, 2019) were used implementing the following R (3.3.2) packages: boot 1.3; hmeasure 1.0; MASS 7.4; mdscore 0.3; matrixStats 0.55.0. The significance level was set at $p \leq 0.05$, 2-tailed.

The Hosmer-Lemeshow test was run for testing each multivariate logistic regression model (Hosmer & Lemeshow, 2000). A p-value > 0.05 suggested a good fit to the data (Hosmer & Lemeshow, 2000). Receiver Operating Characteristic (ROC) analysis was used to estimate the sensitivity and specificity of each model. The area under the ROC curve (AUC) was evaluated as follows: non-informative (AUC = 0.5), less accurate (0.5 < AUC ≤ 0.7), moderately accurate (0.7 < AUC ≤ 0.9), highly accurate (0.9 < AUC < 1), perfect test (AUC = 1) (Swets, 1988). The statistical software MedCalc 14.8.1 was used.

5 Results

5.1 Descriptive Variables: Total Sample

Three hundred subjects were enrolled and equally distributed among subjects with a diagnosis of Chronic Migraine (CM), subjects with a diagnosis of Episodic Migraine (EM), and Healthy Subjects (HS).

Eighty percent (n = 240) of the participants were females, and 20% (n = 60) were males. The same percentage were observed in CM (females = 80%, males = 20%), EM (females = 80%, males = 20%), and HS (females = 80%, males = 20%) due to the gender-matching procedure.

The mean age of the overall sample (n = 300) ± SD was 42.72 ± 11.72 years; no statistically significant differences were observed among the three groups due to the age-matching procedure (Table 3).

Table 3. Mean age. Comparison between chronic migraine, episodic migraine, and healthy subjects. Mann–Whitney *U* test

Group	Age M (±SD)	p
Healthy subjects (n = 100)	43.18 (11.90)	0.603
Episodic migraine (n = 100)	42.34 (11.06)	
Healthy subjects (n = 100)	43.18 (11.90)	0.707
Chronic migraine (n = 100)	42.65 (11.76)	
Episodic migraine (n = 100)	42.34 (11.06)	0.865
Chronic migraine (n = 100)	42.65 (11.76)	

Table 4 shows the frequencies and percentages of sociodemographic characteristics of the total sample. The majority of the subjects were cohabitant or married, had at least a high school education, and was employed as subordinates or employees (Table 4).

Table 4. Sociodemographic characteristics. Total sample (n = 300)

	Total Sample (n = 300)	
Marital status	**n**	**%**
Unmarried	81	27.0
Married	145	48.3
Cohabitant	37	12.3
Separated	23	7.7
Divorced	8	2.7
Widow/er	6	2.0
Total	300	100.0
Educational level	**n**	**%**
Primary school	2	0.7
Secondary school	60	20.0
High school	166	55.3
Bachelor or master degree	58	19.3
Ph.D./post-graduate	14	46.7
Total	300	100.0
Employment	**n**	**%**
Worker or subordinate	43	14.2
Employee	137	45.7
Self-employed	17	5.7
Freelance	20	6.7
Manager/executive	6	2.0
Retired	7	2.3
Student	29	9.7
Unemployed	41	13.7
Total	300	100.0

Table 5 shows anamnestic data of the total sample. The greater part of the subjects reported at least one lifetime hospitalization, daily use of pharmacological therapy, and daily coffee consumption (Table 5). Only 4.4% of subjects reported a substance abuse history, 9.0% received at least one psychotherapy treatment (Table 5).

Table 5. Anamnestic data. Total sample (n = 300)

	Total Sample (n = 300)	
Anamnestic data	**N**	**%**
Past hospitalizations	233	77.7
Comorbidity with other medical disorders	100	33.3
Food/drug allergies	67	22.3
Lifetime psychiatric disorders	75	25.0
Daily use of pharmacological treatments	183	61.0
Daily alcohol consumption	113	37.7
Daily cigarettes consumption	78	26.0
Substance abuse	13	4.4
Daily coffee consumption	246	82.0
Lifetime psychotherapy treatment	27	9.0
Current psychotherapy treatment	78	26.0

5.2 Comparison between Healthy Subjects and Episodic Migraine Subjects

5.2.1 Comparison between Healthy Subjects and Episodic Migraine Subjects: Descriptive Statistics

Table 6 presents the comparisons of sociodemographic characteristics. No statistically significant differences were observed between HS and EM concerning marital status, education, and employment.

Table 6. Comparison between of episodic migraine subjects and healthy subjects (n = 200). Sociodemographic characteristics. Chi-squared test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**		
Marital status	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Unmarried	30 (30.0)	23 (23.0)		
Married	44 (44.0)	52 (52.0)		
Cohabitant	11 (11.0)	16 (16.0)		
Separated	8 (8.0)	6 (6.0)	4.08 (5)	0.440
Divorced	4 (4.0)	1 (1.0)		
Widow/er	3 (3.0)	2 (2.0)		
Total	100 (100.0)	100 (100.0)		
Educational level	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Primary school	0 (0.0)	00 (0.0)		
Secondary school	20 (20.0)	019 (19.0)		
High school	54 (54.0)	062 (62.0)	4.20 (3)	0.240
Bachelor or master degree	18 (18.0)	17 (17.0)		
Ph.D./post-graduate	8 (8.0)	2 (2.0)		
Total	100 (100.0)	100 (100.0)		
Employment	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Worker or subordinate	14 (14.0)	15 (15.0)		
Employee	38 (38.0)	52 (52.0)		
Self-employed	9 (9.0)	6 (6.0)		
Freelance	9 (9.0)	6 (6.0)		
Manager/executive	2 (2.0)	0 (0.0)	7.79 (7)	0.351
Retired	2 (2.0)	3 (3.0)		
Student	11 (11.0)	10 (10.0)		
Unemployed	15 (15.0)	8 (8.0)		
Total	100 (100.0)	100 (100.0)		

Table 7 shows comparisons concerning anamnestic data. HS and EM showed statistically significant differences in food or drug allergies (p = 0.030), daily use of pharmacological treatments (p = 0.000), daily consumption of alcoholic beverages (p = 0.023), and daily cigarette smoking (p = 0.001) (Table 7).

Table 7. Comparison between healthy subjects and episodic migraine subjects (n = 200). Anamnestic data. Chi-squared test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**		
Anamnestic data	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Past hospitalizations	76 (76.6)	76 (76.6)	0.000(1)	1.000
Comorbidity with other medical disorders	27 (27.0)	32 (32.0)	0.601(1)	0.438
Food/drug allergies	17 (17.0)	30 (30.0)	4.700(1)	**0.030**
Lifetime psychiatric disorders	19 (19.0)	20 (20.0)	0.032(1)	0.858
Daily use of pharmacological treatments	38 (38.0)	66 (66.0)	15.705(1)	**0.000**
Daily consumption of alcoholic beverages	53 (53.0)	34 (34.0)	5.172(1)	**0.023**
Daily cigarette smoking	38 (38.0)	17 (17.0)	11.606(1)	**0.001**
Substance abuse	5 (5.0)	1 (1.0)	2.749(1)	0.097
Daily coffee consumption	14 (14.0)	15 (15.0)	1.149(2)	0.563
Lifetime psychotherapy treatment	9 (9.0)	7 (7.0)	3.191(1)	0.074
Current psychotherapy treatment	26 (26.0)	25 (25.0)	0.026(1)	0.871

5.2.2 Comparison between Healthy Subjects and Episodic Migraine: ID Migraine and Migraine Disability Assessment Questionnaire

Table 8 reports the comparisons concerning migraine features measured with the ID Migraine. Statistically significant differences between HS and EM were observed in: presence of migraine (p = 0.000); presence of nausea (p = 0.000); presence of photophobia (p = 0.000); presence of disability due to migraine (p = 0.000). As expected, HS did not show migraine symptoms (Table 8).

Table 8. ID Migraine. Difference between healthy subjects and episodic migraine subjects (n = 200). Chi-squared test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**		
ID Migraine	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Presence of migraine	0 (0.0)	100 (100.0)	200.000 (1)	**0.000**
Presence of nausea	0 (0.0)	67 (67.0)	100.752 (1)	**0.000**
Presence of photophobia	0 (0.0)	76 (76.0)	122.581 (1)	**0.000**
Presence disability	0 (0.0)	70 (70.0)	107.692 (1)	**0.000**

Table 9 shows the comparison concerning the levels of disability assessed via the MIDAS. EM reported higher frequencies of migraine disability in all the MIDAS grades. Statistically significant difference between HS and EM were found in grade I (minimal disability) (p = 0.000), grade II (mild disability) (p = 0.000), grade III (moderate disability) (p = 0.000), and grade IV (severe disability) (p = 0.004) (Table 9).

Table 9. Migraine disability assessment questionnaire. Difference between healthy subjects and episodic migraine subjects (n = 200). Chi-squared test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**		
MIDAS	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Grade I: Minimal disability	0 (0.0)	59 (59.0)	51.572 (1)	**0.000**
Grade II: Mild disability	0 (0.0)	17 (17.0)	18.579 (1)	**0.000**
Grade III: Moderate disability	0 (0.0)	16 (16.0)	17.391 (1)	**0.000**
Grade IV: Severe disability	0 (0.0)	8 (8.0)	8.333 (1)	**0.004**

MIDAS: Migraine Disability Assessment Questionnaire

5.2.3 Comparison between Healthy Subjects and Episodic Migraine: Brief Pain Inventory

Table 10 presents the comparisons between pain severity and pain interference concerning the BPI scores. Statistically significant differences between HS and EM were reported in pain severity (p = 0.000), activity interference (p = 0.000), and affect interference (p = 0.010). The highest levels of BPI scores were observed in episodic migraine subjects (Table 10).

Table 10. Brief pain inventory. Difference between healthy subjects and episodic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**	
Brief Pain Inventory	**M (±SD)**	**M (±SD)**	**p**
Pain Severity	0.00 (0.00)	18.28 (7.51)	**0.000**
Activity Interference	0.00 (0.00)	7.23 (7.37)	**0.022**
Affect Interference	0.00 (0.00)	8.40 (7.78)	**0.010**

5.2.4 Comparison between Healthy Subjects and Episodic Migraine: SCID-5 Diagnoses

Table 11 reports the results of SCID-5 diagnoses. Overall a similar percentage of diagnosis was observed in HS (25%) and EM (26%) (Table 11). In the HS, 15% endorsed the criteria for one DSM-5 disorder and 4% reported comorbidity of one or more disorders. Similarly, 18% of EM fulfilled the criteria for one DSM-5 disorder and 3% showed comorbidity of one or more disorders (Table 11). The HS showed the highest rates of social anxiety disorder and panic disorder (Table 11). On the opposite, EM showed the highest rates of major depressive disorder and agoraphobia (Table 11). A statistically significant difference was observed concerning the diagnosis of generalized anxiety disorder (GAD) ($p = 0.043$) (Table 11). Four HS reported a diagnosis of GAD, whereas no EM fulfilled the diagnosis of GAD (Table 11).

Table 11. Frequencies of SCID-5 diagnoses. Difference between healthy subjects and episodic migraine subjects (n = 200). Chi-squared test; Kruskal–Wallis test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**		
SCID-5	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Agoraphobia	2 (2.0)	8 (8.0)	3.798 (1)	0.052
Social Anxiety Disorder	4 (4.0)	1 (1.0)	1.846 (1)	0.174
Panic Disorder	9 (9.0)	5 (5.0)	1.229 (1)	0.268
Specific Phobia	2 (2.0)	1 (1.0)	0.338 (1)	0.561
Generalized Anxiety Disorder	4 (4.0)	0 (0.0)	4.082 (1)	**0.043**
Major Depressive Disorder	2 (2.0)	6 (6.0)	2.083 (1)	0.149
Persistent Depressive Disorder	0 (0.0)	0 (0.0)	-	-
Obsessive-Compulsive Disorder	1 (1.0)	2 (2.0)	0.338 (1)	0.561
Posttraumatic Stress Disorder	0 (0.0)	0 (0.0)	-	-
Body Dysmorphic Disorder	0 (0.0)	1 (1.0)	1.005 (1)	0.316
Illness Anxiety Disorder	1 (1.0)	0 (0.0)	1.005 (1)	0.316
Bipolar Disorder	0 (0.0)	1 (1.0)	1.005 (1)	0.316
Total number of SCID-5 diagnoses	25 (25.0)	26 (26.0)	0.026 (1)	0.873
SCID-5 comorbidity	**n (%)**	**n (%)**	-	**p**
1 SCID-5 diagnosis	15 (15.0)	18 (18.0)		
2 SCID-5 diagnoses	2 (2.0)	2 (2.0)		0.779
3 SCID-5 diagnoses	2 (2.0)	6 (6.0)		

SCID-5: Structured Clinical Interview for DSM-5 disorders

5.2.5 Comparison between Healthy Subjects and Episodic Migraine: DCPR-R-ISS Diagnoses

Table 12 presents the comparison of DCPR-R-ISS diagnoses. Overall, a higher percentage of diagnosis was observed in EM (90%) than HS (80%) ($p = 0.048$) (Table 12). Nineteen percent of HS showed a comorbidity with one or more psychosomatic disorders, and 27% of the EM showed DCPR-R comorbidity (Table 12). EM showed the highest rates of DCPR-R diagnosis in the cluster of illness behaviour, concerning illness denial, persistent somatization, conversion symptoms, and anniversary reaction (Table 12). A statistically significant difference was found in illness denial ($p = 0.007$) (Table 12). Seven EM reported a diagnosis of Illness denial, whereas no HS fulfilled the diagnosis of Illness denial (Table 12). Similarly, EM showed a higher percentage of allostatic overload, even though the difference was not statistically significant (Table 12). On the contrary, HS showed the highest rates of DCPR-R diagnosis in the cluster of personality and psychological manifestations, but without statistically significant differences (Table 12).

Table 12. Frequencies of DCPR-R-SSI diagnoses. Difference between healthy subjects and episodic migraine subjects (n = 200). Chi-squared test; Kruskal–Wallis test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**		
DCPR-R-SSI	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Allostatic Overload	14 (14.0)	24 (24.0)	3.249 (1)	0.071
Health Anxiety	11 (11.0)	5 (5.0)	2.446 (1)	0.118
Disease Phobia	0 (0.0)	1 (1.0)	1.005 (1)	0.316
Hypochondriasis	3 (3.0)	2 (2.0)	0.205 (1)	0.651
Thanatophobia	3 (3.0)	2 (2.0)	2.020 (1)	0.155
Illness Denial	0 (0.0)	7 (7.0)	7.254 (1)	**0.007**
Persistent Somatization	3 (2.0)	5 (5.0)	0.521 (1)	0.470
Conversion Symptoms	2 (2.0)	7 (7.0)	2.857 (1)	0.091
Anniversary Reaction	2 (2.0)	5 (5.0)	1.132 (1)	0.248
Demoralization	4 (4.0)	5 (5.0)	0.116 (1)	0.733
Irritable Mood	10 (10.0)	4 (4.0)	2.756 (1)	0.096
Type A Behavior	21 (21.0)	13 (13.0)	2.268 (1)	0.132
Alexithymia	12 (12.0)	10 (10.0)	0.204 (1)	0.651
Total number of DCPR-R-ISS diagnoses	80 (80.0)	90 (90.0)	3.992 (1)	**0.048**
DCPR-R-SSI comorbidity	**n (%)**	**n (%)**	-	**p**
1 DCPR-R-SSI diagnosis	32 (32.0)	26 (26.0)		
2 DCPR-R-SSI diagnoses	24 (24.0)	40 (40.0)		
3 DCPR-R-SSI diagnoses	18 (18.0)	15 (15.0)		0.889
4 DCPR-R-SSI diagnoses	4 (4.0)	4 (4.0)		
5 DCPR-R-SSI diagnoses	0 (0.0)	5 (5.0)		

DCPR-R-SSI: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview

5.2.6 Comparison between Healthy Subjects and Episodic Migraine: Clinical Interview for Depression

Table 13 shows the results of the CID. The differences were statistically significant for: guilt, lowered self-esteem, and worthlessness ($p = 0.002$); phobic anxiety ($p = 0.011$); avoidance, main phobia ($p = 0.025$); retardation ($p = 0.030$); work and interests ($p = 0.001$); agitation ($p = 0.030$) (Table 13). Overall, EM had higher mean CID scores except for guilt, lowered self-esteem, and worthlessness; work and interests; agitation; that showed higher statistically significant scores in the group of HSs (Table 13).

Table 13. Clinical Interview for Depression. Difference between healthy subjects and episodic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	Episodic migraine (n = 100)	
Clinical Interview for Depression	**M (±SD)**	**M (±SD)**	**p**
Feelings of depressed mood	1.57 (0.97)	01.80 (1.14)	0.127
Guilt, lowered self-esteem, and worthlessness	2.12 (0.97)	01.70 (1.15)	**0.002**
Pessimism and hopelessness	1.17 (0.53)	1.30 (0.83)	0.366
Suicidal tendencies	1.22 (0.89)	1.14 (0.59)	0.594
Work and interests	1.74 (0.98)	1.39 (0.87)	**0.001**
Energy and fatigue	1.64 (0.92)	1.84 (1.07)	0.217
Anxiety psychic, generalized	1.69 (1.09)	1.77 (1.11)	0.661
Panic attacks	1.11 (0.40)	1.05 (0.30)	0.270
Phobic anxiety	1.31 (0.69)	1.72 (1.19)	**0.011**
Avoidance, main phobia	1.26 (0.79)	1.71 (1.46)	**0.025**
Anxiety somatic	1.47 (0.88)	1.31 (0.69)	0.208
Anorexia	1.06 (0.28)	1.17 (0.55)	0.163
Increased appetite	1.17 (0.45)	1.17 (0.53)	0.477
Irritability	1.45 (0.72)	1.35 (0.61)	0.275
Initial insomnia	1.36 (0.81)	1.41 (0.87)	0.630
Delayed insomnia	1.55 (0.96)	1.67 (1.17)	0.895
Hostility	1.01 (0.10)	1.02 (0.20)	0.648
Retardation	1.02 (0.14)	1.10 (0.33)	**0.030**
Agitation	1.22 (0.54)	1.07 (0.29)	**0.014**
Depressed appearance	1.07 (0.29)	1.17 (0.51)	0.185
Total score depressive symptoms	20.75 (4.85)	21.55 (6.19)	0.693
Total score anxiety	5.37 (2.03)	6.25 (2.96)	0.054

5.2.7 Comparison between Healthy Subjects and Episodic Migraine: Mental Pain Questionnaire

Table 14 reports the results of the MPQ. EM showed a higher MPQ mean score than HS, however, this difference was not statistically significant (Table 14).

Table 14. Mental Pain Questionnaire. Difference between healthy subjects and episodic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**	
	M (±SD)	**M (±SD)**	**p**
Mental Pain Questionnaire	0.94 (1.59)	1.05 (1.55)	0.407

5.2.8 Comparison between Healthy Subjects and Episodic Migraine: Euthymia Scale

Table 15 shows the results of the ES. EM had lower ES scores in both psychological flexibility and psychological well-being scores than HS. This difference was not statistically significant (Table 15).

Table 15. Euthymia Scale. Difference between healthy subjects and episodic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**	
Euthymia Scale	**M (±SD)**	**M (±SD)**	**p**
Psychological Flexibility	4.16 (1.18)	4.01 (1.01)	0.095
Psychological Well-being	3.51 (1.34)	3.33 (1.13)	0.282

5.2.9 Comparison between Healthy Subjects and Episodic Migraine: PsychoSocial Index

Table 16 presents the results of the PsychoSocial Index. EM showed statise tically significant higher levels of psychological distress than HS (p = 0.000) (Table 16). EM showed statistically significant lower levels of quality of life than HS (p = 0.009) (Table 16).

Table 16. PsychoSocial Index. Difference between healthy subjects and episodic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Episodic migraine (n = 100)**	
PsychoSocial Index	**M (±SD)**	**M (±SD)**	**p**
Well-being	4.98 (1.05)	4.98 (1.09)	0.953
Stress	2.15 (1.97)	2.15 (1.74)	0.738
Psychological Distress	4.81 (4.37)	7.30 (4.35)	**0.000**
Abnormal Illness Behaviour	0.55 (1.10)	0.35 (0.70)	0.250
Quality of Life	2.93 (0.69)	2.67 (0.64)	**0.009**

5.2.10 Univariate and Multivariate Model of Protective and Risk Factors for Episodic Migraine

5.2.10.1 Skewness and Kurtosis of Anamnestic, Psychosocial and Psychiatric Variables

Table 17 reports the values of skewness and kurtosis for the anamnestic data (i.e., food or drug allergies daily use of pharmacological treatments, daily consumption of alcoholic beverages, daily cigarette smoking). The values of skewness and kurtosis were found to be in the range of acceptability, thus they were included in both univariate and multivariate logistic regression models as correction variables.

Table 18 showed the values of skewness and kurtosis for psychiatric and psychosocial rating scales (i.e., number of SCID-5 diagnoses; number of DCPR-R-ISS diagnoses; CID depressive symptoms; CID anxiety; MPQ total score; ES psychological flexibility; ES psychological well-being; PSI well-being; PSI stress; PSI psychological distress; PSI abnormal illness behaviour; PSI quality of life). All the rating scale scores showed value in the range of acceptability, thus they were selected for the univariate and multivariate logistic regression analyses.

Table 17. Comparison between healthy subjects and episodic migraine subjects (n = 200). Anamnestic data. Skewness and kurtosis

	Total (n = 200)		**Healthy subjects (n = 100)**		**Episodic migraine (n = 100)**	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Food/drug allergies	1.26	-0.42	1.78	1.21	0.89	-1.24
Daily use of pharmacological treatments	-0.08	-2.01	0.50	-1.78	-0.70	1.56
Daily alcohol consumption	0.20	-1.97	-0.12	-2.01	0.55	1.74
Daily cigarette smoking	1.01	-0.97	0.24	-1.78	0.24	1.21

Table 18. Comparison between of healthy subjects and episodic migraine subjects (n = 200). Psychosocial and psychiatric variables. Skewness and kurtosis

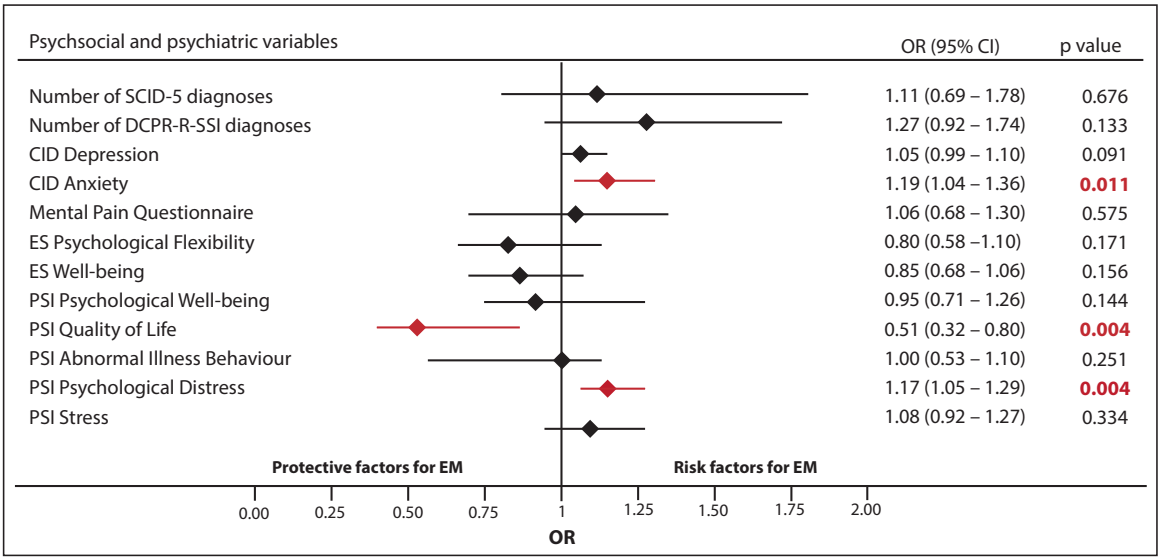
	Total (n =200)		Healthy subjects (n = 100)		Episodic migraine (n = 100)	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Number of SCID-5 diagnoses	2.83	2.93	2.84	2.74	2.86	2.76
Number of DCPR-R-ISS diagnoses	1.18	1.25	1.15	0.84	1.19	1.45
CID total score depressive symptoms	1.53	2.41	1.26	1.71	1.58	2.51
CID total score anxiety	1.81	2.49	1.63	2.52	1.64	2.45
Mental Pain Questionnaire	2.06	2.57	2.15	2.36	1.62	2.18
ES Psychological Flexibility	-1.44	2.19	-1.90	2.72	-0.84	1.19
ES Psychological Well-being	-0.70	-0.23	-0.77	-0.13	-0.65	-0.26
PSI Well-being	-1.02	0.76	-0.96	0.39	-1.10	1.16
PSI Stress	1.02	1.30	1.26	2.27	0.66	-0.34
PSI Psychological Distress	1.40	2.90	2.26	2.89	0.94	0.78
PSI Abnormal Illness Behaviour	2.31	2.95	2.17	2.90	2.07	2.37
PSI Quality of Life	-0.44	0.47	-0.29	0.17	-0.87	0.67

SCID-5: Structured Clinical Interview for DSM-5 disorders. DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID: Clinical Interview for Depression; ES: Euthymia Scale; PSI: PsychoSocial-Index

5.2.10 .2 Univariate Models of Protective and Risk Factors for Episodic Migraine as compared to Healthy Subjects

Figure 8 shows the results of univariate logistic regressions. When EM were compared to HS, CID anxiety (OR = 1.19; 95% CI = 1.04–1.36; p = 0.011) and PSI psychological distress (OR = 1.17; 95% CI = 1.05–1.29; p = 0.004) were found to be statistically significant risk factors for being EM if compared to HS (Figure 8). PSI quality of life was found a statistically significant protective factor (OR = 0.51; 95% CI = 0.32–1.80; p = 0.004) (Figure 8).

Figure 8. Univariate Logistic regressions for episodic migraine subjects as compared to healthy subjects, adjusted for food/drug allergies, daily use of pharmacological treatments, daily alcohol consumption, daily cigarette smoking (n = 200)



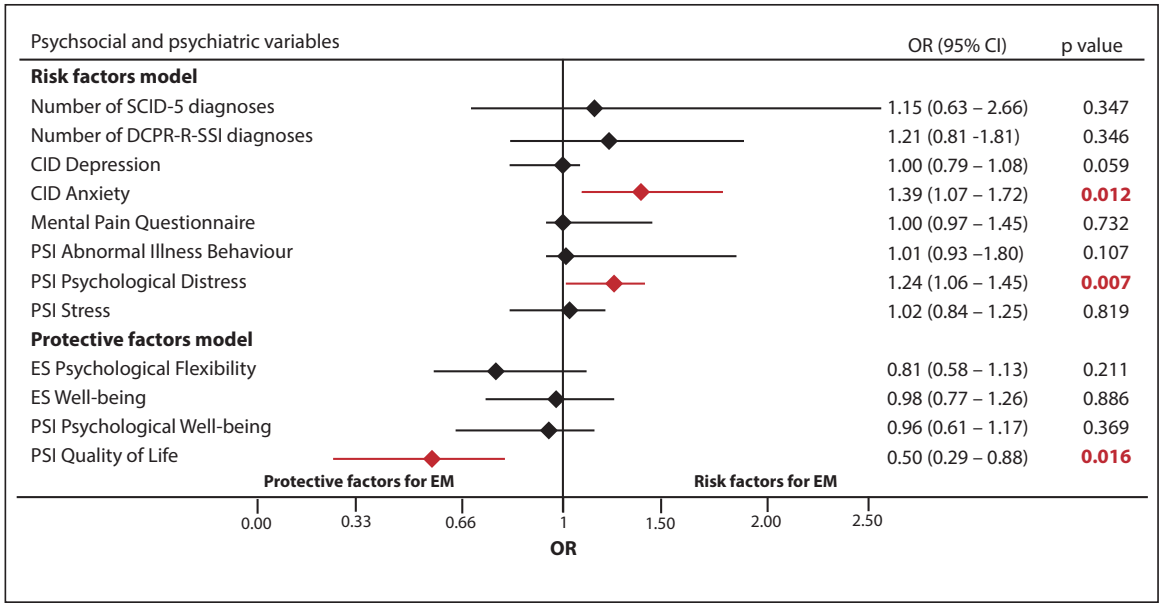
SCID-5: Structured Clinical Interview for DSM-5 disorders; DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID Depression: Clinical Interview for Depression total score depressive symptoms; CID Anxiety: Clinical Interview for Depression total score anxiety; ES: Euthymia Scale; PSI: PsychoSocial-Index; EM: episodic migraine

5.2.10.3 Multivariate Model of Risk and Protective Factors for Episodic Migraine as compared to Healthy Subjects

Figure 9 shows multivariate model of risk factors for being EM if compared to HS. CID anxiety (OR = 1.39; 95% CI = 1.07–1.72; p = 0.012) and PSI psychological distress (OR = 1.24; 95% CI = 1.06–1.45; p = 0.007) were found as risk factors for EM as compared to HS (Figure 9). Homser and Lemeshow test indicated that data fit with logistic regression model (χ^2 = 8.19; df = 8; p = 0.413). The AUC under de ROC curve was found moderately accurate (AUC = 0.81) with sensitivity 0.73 and specificity 0.75.

Figure 9 shows the multivariate model for protective factors for EM. PSI Quality of life was found as protective factor for EM as compared to HS (OR = 0.50; 95% CI = 0.29–0.88; p = 0.016) (Figure 9). Homser and Lemeshow test indicated that data fit with logistic regression model (χ^2 = 9.19; df = 8; p = 0.274). The AUC under de ROC curve was found moderately accurate (AUC = 0.76) with sensitivity 0.74 and specificity 0.67.

Figure 9. Multivariate Logistic regressions for episodic migraine subjects as compared to healthy subjects adjusted for food/drug allergies, daily use of pharmacological treatments, daily alcohol consumption, daily cigarette smoking (n = 200). Models of risk factors and protective factors



SCID-5: Structured Clinical Interview for DSM-5 disorders; DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID Depression: Clinical Interview for Depression total score depressive symptoms; CID Anxiety: Clinical Interview for Depression total score anxiety; ES: Euthymia Scale; PSI: PsychoSocial-Index; EM: episodic migraine

5.3 Comparison between Healthy Subjects and Chronic Migraine Subjects

5.3.1 Comparison between Healthy Subjects and Chronic Migraine Subjects: Descriptive Variables

Table 19 presents the comparisons concerning sociodemographic characteristics. No statistically significant differences were observed between HS and CM concerning marital status, education, and employment.

Table 19. Comparison between healthy subjects and chronic migraine subjects (n = 200). Sociodemographic characteristics. Chi-squared test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**		
Marital status	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Unmarried	30 (30.0)	28 (28.0)		
Married	44 (44.0)	49 (49.0)		
Cohabitant	11 (11.0)	10 (10.0)		
Separated	8 (8.0)	9 (9.0)	1.58 (5)	1.000
Divorced	4 (4.0)	3 (3.0)		
Widow/er	3 (3.0)	1 (1.0)		
Total	100 (100.0)	100 (100.0)		
Educational level	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Primary school	0 (0.0)	2 (2.0)		
Secondary school	20 (20.0)	21 (21.0)		
High school	54 (54.0)	50 (50.0)	4.21 (4)	0.891
Bachelor or master degree	18 (18.0)	23 (23.0)		
Ph.D./post-graduate	8 (8.0)	4 (4.0)		
Total	100 (100.0)	100 (100.0)		
Employment	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Worker or subordinate	14 (14.0)	14 (14.0)		
Employee	38 (38.0)	47 (47.0)		
Self-employed	9 (9.0)	2 (2.0)		
Freelance	9 (9.0)	5 (5.0)		
Mangaer/executive	2 (2.0)	4 (4.0)	7.96 (7)	0.695
Retired	2 (2.0)	2 (2.0)		
Student	11 (11.0)	8 (8.0)		
Unemployed	15 (15.0)	18 (18.0)		
Total	100 (100.0)	100 (100.0)		

Table 20 shows comparisons of anamnestic data. Statistically significant differences were found between HS and EM in lifetime psychiatric disorders (p = 0.007), daily use of pharmacological treatments (p = 0.000), daily consumption of alcoholic beverages (p = 0.000), and daily cigarette smoking (p = 0.021) (Table 20).

Table 20. Comparison between healthy subjects and chronic migraine subjects (n = 200). Anamnestic data. Chi-squared test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**		
Anamnestic data	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Past hospitalizations	76 (76.0)	81 (81.0)	0.741 (1)	**0.398**
Comorbidity with other medical disorders	27 (27.0)	41 (41.0)	4.367 (1)	**0.037**
Food/drug allergies	17 (17.0)	20 (20.0)	0.298 (1)	0.585
Lifetime psychiatric disorders	19 (19.0)	36 (36.0)	7.248 (1)	**0.007**
Daily use of pharmacological treatments	38 (38.0)	79 (79.0)	38.531 (1)	**0.000**
Daily alcohol consumption	53 (53.0)	26 (26.0)	15.253 (1)	**0.000**
Daily cigarette smoking	38 (38.0)	23 (23.0)	5.301 (1)	**0.021**
Substance abuse	5 (5.0)	5 (5.0)	0.000 (1)	**1.000**
Daily coffee consumption	86 (86.0)	75 (75.0)	3.824 (1)	0.052
Lifetime psychotherapy treatment	9 (9.0)	11 (11.0)	0.222 (1)	0.637
Current psychotherapy treatment	26 (26.0)	27 (27.0)	0.026 (1)	0.873

5.3.2 Comparison between Healthy Subjects and Chronic Migraine: ID Migraine and Migraine Disability Assessment Questionnaire

Table 21 reports the comparisons of ID migraine scores. Statistically significant differences between HS and CM were observed in presence of migraine (p = 0.000), presence of nausea (p = 0.000), presence of photophobia (p = 0.000), and presence of disability due to migraine (p = 0.000). Again, HS did not show migraine symptoms (Table 21).

Table 21. ID Migraine. Difference between healthy subjects and chronic migraine subjects (n = 200). Chi-squared test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**		
ID Migraine	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Presence of migraine	0 (0.0)	100 (100.0)	200 .000 (1)	**0.000**
Presence of photophobia	0 (0.0)	60 (60.0)	85.714 (1)	**0.000**
Presence of nausea	0 (0.0)	77 (77.0)	125.203 (1)	**0.000**
Presence disability	0 (0.0)	82 (82.0)	138.983 (1)	**0.000**

Table 22 shows the comparison concerning the levels of disability assessed via the MIDAS. CM subjects reported higher frequencies of migraine disability in all the MIDAS grades (Table 22). Statistically significant differences were found in grade I (minimal disability) (p = 0.000), grade II (mild disability) (p = 0.000), grade III (moderate disability) (p = 0.000), and grade IV (severe disability) (p = 0.000) (Table 22).

Table 22. Migraine Disability Assessment Questionnaire. Difference between healthy subjects and chronic migraine subjects (n = 200). Chi-squared test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**		
MIDAS	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Grade I: Minimal disability	0 (0.0)	23 (23.0)	125.203 (1)	**0.000**
Grade II: Mild disability	0 (0.0)	17 (17.0)	18.579 (1)	**0.000**
Grade III: Moderate disability	0 (0.0)	17 (17.0)	18.579 (1)	**0.000**
Grade IV: Severe disability	0 (0.0)	43 (43.0)	54.777 (1)	**0.000**

MIDAS: Migraine disability assessment questionnaire

5.3.3 Comparison between Healthy Subjects and Chronic Migraine: Brief Pain Inventory

Table 23 presents comparisons concerning pain severity and pain interference assessed with the BPI. Statistically significant differences were reported in pain severity (p = 0.000), activity interference (p = 0.001), and affect interference (p = 0.001) (Table 23). The highest levels of BPI scores were observed in CM (Table 23).

Table 23. Brief pain inventory. Difference between chronic migraine subjects and healthy subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**	
Brief Pain Inventory	**M (±SD)**	**M (±SD)**	**p**
Pain Severity	0.00 (0.00)	23.11 (10.41)	**0.000**
Activity Interference	0.00 (0.00)	11.22 (9.06)	**0.001**
Affect Interference	0.00 (0.00)	13.21 (9.19)	**0.000**

5.3.4 Comparison between Healthy Subjects and Chronic Migraine: SCID-5 Diagnoses

Table 24 reports the comparison on SCID-5 diagnoses. Overall CM reported a higher percentage of SCID-5 diagnoses (37%) than HS (25%) ($p = 0.048$) (Table 24). CM showed a higher percentage of comorbidity than HS, however, this difference was not statistically significant (Table 24). A statistically significant difference was observed in the diagnosis of major depressive disorder (MDD) ($p = 0.017$) (Table 24). Ten percent of CM reported a diagnosis of MDD, whereas 2% of HS fulfilled the DSM-5 criteria for MDD (Table 24).

Table 24. Frequencies of SCID-5 diagnoses. Difference between healthy subjects and chronic migraine subjects (n = 200). Chi-squared test. Kruskal–Wallis test

	Healthy subjects (n = 100)	**Chronic Migraine (n = 100)**		
SCID-5	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Agoraphobia	2 (2.0)	7 (7.0)	2.909 (1)	0.088
Social Anxiety Disorder	4 (4.0)	3 (3.0)	0.148 (1)	0.700
Panic Disorder	9 (9.0)	6 (6.0)	0.649 (1)	0.421
Specific Phobia	2 (2.0)	2 (2.0)	0.000 (1)	1.000
Generalized Anxiety Disorder	4 (4.0)	2 (2.0)	0.687 (1)	0.407
Major Depressive Disorder	2 (2.0)	10 (10.0)	5.674 (1)	**0.017**
Persistent Depressive Disorder	0 (0.0)	2 (2.0)	2.020 (1)	0.155
Obsessive-Compulsive Disorder	1 (1.0)	1 (1.0)	0.000 (1)	1.000
Posttraumatic Stress Disorder	0 (0.0)	2 (2.0)	2.020 (1)	0.155
Body Dysmorphic Disorder	0 (0.0)	1 (1.0)	1.005 (1)	0.316
Illness Anxiety Disorder	1 (1.0)	0 (0.0)	1.005 (1)	0.316
Bipolar Disorder	0 (0.0)	1 (1.0)	1.005 (1)	0.316
Total number of SCID-5 diagnoses	25 (25.0)	37 (37.0)	3.916 (1)	**0.048**
SCID-5 comorbidity	**n (%)**	**n (%)**	-	**p**
1 SCID-5 diagnosis	15 (15.0)	18 (18.0)		
2 SCID-5 diagnoses	2 (2.0)	8 (8.0)		0.186
3 SCID-5 diagnoses	2 (2.0)	1 (1.0)		

SCID-5: Structured Clinical Interview for DSM-5 disorders

5.3.5 Comparison between Healthy Subjects and Chronic Migraine: DCPR-R-ISS Diagnoses

Table 25 presents the comparison of DCPR-R-ISS diagnoses. Overall, a similar percentage of diagnosis was observed in HS (80%) and CM (83%); 19% of the HS showed comorbidity with one or more psychosocial disorders and 25% of the CM showed DCPR-R comorbidity (Table 25). This difference was not statistically significant. CM showed a statistically significant higher percentage of allostatic overload ($p = 0.004$), persistent somatization ($p = 0.009$), and illness denial ($p = 0.003$) (Table 25). On the contrary, HS showed statistically significant higher rates of health anxiety and type A behaviour ($p = 0.009$) than CM (Table 25). Moreover, CM showed higher percentage of demoralization and HS higher percentage of alexithymia, however, these differences were not statistically significant (Table 25).

Table 25. Frequencies of DCPR-R-SSI diagnoses. Difference between healthy subjects and chronic migraine outpatients (n = 200). Chi-squared test. Kruskal–Wallis test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**		
DCPR-R-SSI	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Allostatic Overload	14 (14.0)	31 (31.0)	8.287 (1)	**0.004**
Health Anxiety	11 (11.0)	1 (1.0)	8.865 (1)	**0.003**
Disease Phobia	1 (1.0)	2 (2.0)	2.020 (1)	0.155
Hypochondriasis	3 (3.0)	3 (3.0)	0.000 (1)	1.000
Thanatophobia	3 (3.0)	2 (2.0)	2.020 (1)	0.155
Illness Denial	0 (0.0)	6 (6.0)	6.186 (1)	**0.013**
Persistent Somatization	3 (1.0)	13 (13.0)	6.793 (1)	**0.009**
Conversion Symptoms	2 (2.0)	1 (1.0)	0.349 (1)	0.555
Anniversary Reaction	2 (2.0)	3 (3.0)	0.205 (1)	0.651
Demoralization	4 (4.0)	11 (11.0)	3.532 (1)	0.060
Irritable Mood	10 (10.0)	13 (13.0)	0.442 (1)	0.506
Type A Behavior	21 (21.0)	8 (8.0)	6.816 (1)	**0.009**
Alexithymia	12 (12.0)	5 (5.0)	3.150 (1)	0.076
Total number of DCPR-R-ISS diagnoses	80 (80.0)	83 (83.0)	0.298 (1)	0.585
DCPR-R-SSI comorbidity	**n (%)**	**n (%)**	**-**	**p**
1 DCPR-R-SSI diagnosis	34 (34.0)	37 (37.0)		
2 DCPR-R-SSI diagnoses	12 (12.0)	16 (16.0)		
3 DCPR-R-SSI diagnoses	6 (6.0)	7 (7.0)		0.710
4 DCPR-R-SSI diagnoses	1 (1.0)	1 (1.0)		
5 DCPR-R-SSI diagnoses	0 (0.0)	1 (1.0)		

DCPR-R-SSI: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview

5.3.6 Comparison between Healthy Subjects and Chronic Migraine. Clinical Interview for Depression

Table 26 shows the results concerning the CID. Overall, CM had higher mean item and subscale scores with the exception of CID panic attacks that was found to be higher in HS than CM (Table 26). The differences were statistically significant for: feelings of depressed mood ($p = 0.002$); guilt, lowered self-esteem, and worthlessness ($p = 0.001$); pessimism and hopelessness ($p = 0.001$); suicidal tendencies ($p = 0.031$); energy and fatigue ($p = 0.031$); panic attacks ($p = 0.000$); phobic anxiety ($p = 0.004$); anxiety somatic ($p = 0.008$); anorexia ($p = 0.019$); delayed insomnia ($p = 0.003$); retardation ($p = 0.009$); depressed appearance ($p = 0.012$); total score depressive symptoms ($p = 0.004$); total score anxiety ($p = 0.002$) (Table 26).

Table 26. Clinical Interview for Depression. Difference between healthy subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**	
Clinical Interview for Depression	**M (±SD)**	**M (±SD)**	**p**
Feelings of depressed mood	1.57 (0.97)	2.00 (1.12)	**0.002**
Guilt, lowered self-esteem, and worthlessness	2.12(0.97)	2.02 (1.30)	0.308
Pessimism and hopelessness	1.17 (0.53)	1.64 (1.20)	**0.001**
Suicidal tendencies	1.22 (0.89)	1.38 (0.88)	**0.031**
Work and interests	1.74 (0.98)	1.79 (1.15)	0.756
Energy and fatigue	1.64 (0.92)	2.37 (1.36)	**0.031**
Anxiety psychic, generalized	1.69 (1.09)	2.17 (1.26)	0.756
Panic attacks	1.11 (0.40)	1.06 (0.42)	**0.000**
Phobic anxiety	1.31 (0.69)	1.72 (1.14)	**0.004**
Avoidance, main phobia	1.26 (0.79)	1.67 (1.36)	0.124
Anxiety somatic	1.47 (0.88)	1.89 (1.50)	**0.008**
Anorexia	1.06 (0.28)	1.29 (0.62)	**0.019**
Increased appetite	1.17 (0.45)	1.24 (0.67)	0.161
Irritability	1.45 (0.72)	1.41 (0.79)	0.979
Initial insomnia	1.36 (0.81)	1.86 (1.33)	0.291
Delayed insomnia	1.55 (0.96)	1.86 (1.38)	**0.003**
Hostility	1.01 (0.10)	1.05 (0.41)	0.690
Retardation	1.02 (0.14)	1.16 (0.49)	**0.009**
Agitation	1.22 (0.54)	1.12 (0.41)	0.165
Depressed appearance	1.07 (0.29)	1.27 (0.65)	**0.012**
Total score depressive symptoms	20.75 (4.85)	24.29 (7.48)	**0.001**
Total score anxiety	5.37 (2.03)	6.62 (3.04)	**0.002**

5.3.7 Comparison between Healthy Subjects and Chronic Migraine: Mental Pain Questionnaire

Table 27 reports the results of the MPQ. CM showed a statistically significant higher MPQ mean score than HS (p = 0.000) (Table 27).

Table 27. Mental Pain Questionnaire. Difference between healthy subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**	
	M (±SD)	**M (±SD)**	**p**
Mental Pain Questionnaire	0.94 (1.59)	2.44 (2.46)	**0.000**

5.3.8 Comparison between Healthy Subjects and Chronic Migraine: Euthymia Scale

Table 28 shows the results of the Euthymia Scale. The CM had statistically significant lower ES scores than HS in both psychological flexibility (p = 0.003) and psychological well-being (p = 0.000) scores (Table 28).

Table 28. Euthymia Scale. Difference between healthy subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**	
Euthymia Scale	**M (±SD)**	**M (±SD)**	**p**
Psychological Flexibility	4.16 (1.18)	3.84 (1.03)	**0.003**
Psychological Well-being	3.51 (1.34)	2.57 (1.50)	**0.000**

5.3.9 Comparison between Healthy Subjects and Chronic migraine: PsychoSocial Index

Table 29 presents the results of the PsychoSocial Index. CM showed statistically significant higher levels of psychological distress than HS (p = 0.000) (Table 29). On the contrary, CM showed statistically significant lower levels of well-being (p = 0.009) and quality of life (p = 0.000) than HS (Table 29).

Table 29. PsychoSocial Index. Difference between healthy subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Healthy subjects (n = 100)	**Chronic migraine (n = 100)**	
PsychoSocial Index	**M (±SD)**	**M (±SD)**	**p**
Well-being	4.98 (1.05)	4.49 (1.32)	**0.009**
Stress	2.15 (1.97)	2.49 (2.05)	0.232
Psychological Distress	4.81 (4.37)	10.70 (6.70)	**0.000**
Abnormal Illness Behaviour	0.55 (1.10)	0.60 (0.91)	0.303
Quality of Life	2.93 (0.69)	2.44 (0.91)	**0.000**

5.3.10 Comparison between Healthy Subjects and Chronic Migraine: Univariate and Multivariate Logistic Regressions

5.3.10.1 Skewness and Kurtosis of Anamnestic, Psychosocial, and Psychiatric Variables

Table 30 reports the values of skewness and kurtosis for the anamnestic data (i.e., in food or drug allergies, daily use of pharmacological treatments, daily consumption of alcoholic beverages, daily cigarette smoking). The values of skewness and kurtosis were found in the range of acceptability, thus they were included in both univariate and multivariate logistic regressions as adjusting variables (Table 30).

Table 31 showed the values of skewness and kurtosis for psychiatric and psychosocial rating scales (i.e., number of SCID-5 diagnoses; number of DCPR-R-ISS diagnoses; CID depressive symptoms; CID anxiety; Mental Pain Questionnaire; ES psychological flexibility; ES psychological well-being; PSI well-being; PSI stress; PSI psychological distress; PSI abnormal illness behaviour; PSI quality of life). All the rating scale scores showed value in the range of acceptability, thus they were selected for univariate and multivariate logistic regression analyses (Table 31).

Table 30. Comparison between of healthy subjects and chronic migraine subjects (n = 200). Anamnestic data. Skewness and kurtosis

	Total (n =200)		**Healthy subjects (n = 100)**		**Chronic migraine (n = 100)**	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Lifetime psychiatric disorders	1.01	-0.98	1.60	0.56	0.59	-1.69
Daily use of pharmacological treatments	-0.35	-1.90	0.50	-1.78	-1.44	0.09
Daily alcohol consumption	0.43	-1.83	-0.12	-2.03	1.11	-0.79
Daily cigarettes consumption	0.85	-1.28	0.50	-1.78	1.30	0.48

Table 31. Comparison between of healthy subjects and chronic migraine subjects (n = 200). Psychosocial and psychiatric variables. Skewness and kurtosis

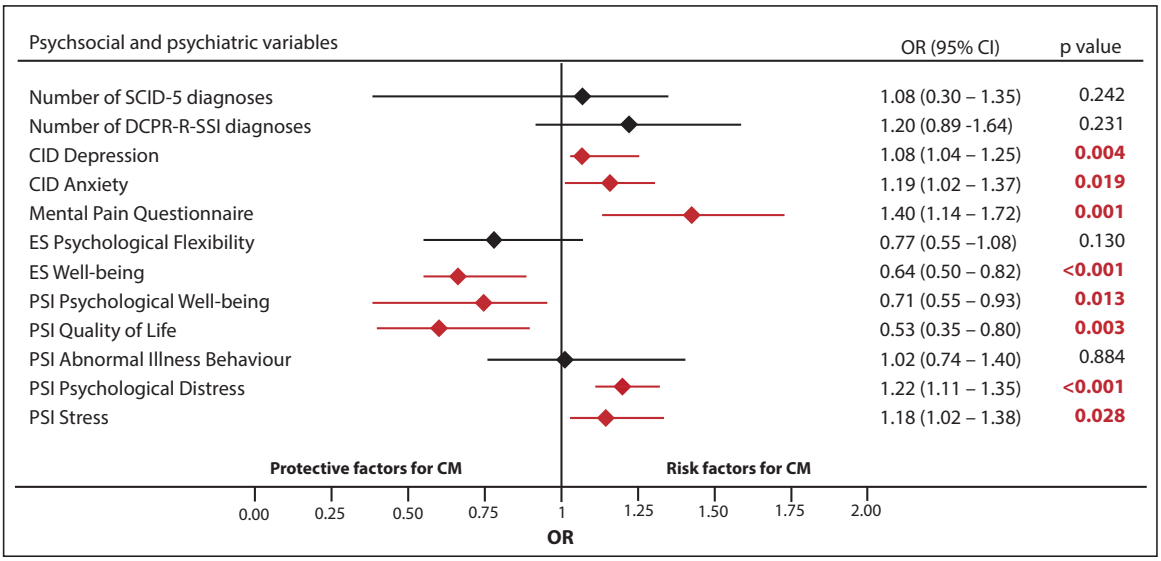
	Total (n =200)		Healthy subjects (n = 100)		Chronic migraine (n = 100)	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Number of SCID-5 diagnoses	2.25	2.87	2.64	1.52	2.76	2.64
Number of DCPR-R-ISS diagnoses	1.17	1.03	1.15	0.84	1.18	1.58
CID total score depressive symptoms	1.18	1.02	1.22	1.71	0.84	-0.05
CID total score anxiety	1.78	2.98	1.68	2.52	1.26	2.90
Mental Pain Questionnaire	1.45	1.58	2.15	2.36	0.98	0.35
ES Psychological Flexibility	-1.31	1.71	-1.90	2.72	-0.68	-0.26
ES Psychological Well-being	-0.45	-0.73	-0.77	-0.13	-0.15	-0.87
PSI Well-being	-0.79	-0.04	-0.96	0.39	-0.57	-0.43
PSI Stress	0.97	0.80	1.26	2.27	0.73	-0.19
PSI Psychological Distress	1.18	1.37	2.26	2.92	0.64	0.32
PSI Abnormal Illness Behaviour	1.96	2.02	2.17	2.90	1.70	1.94
PSI Quality of Life	-0.42	0.17	-0.29	0.17	-0.18	-0.10

SCID-5: Structured Clinical Interview for DSM-5 disorders. DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID: Clinical Interview for Depression; ES: Euthymia Scale; PSI: PsychoSocial-Index

5.3.10.2 Univariate Models of Protective and Risk Factors for Chronic Migraine as compared to Healthy Subjects

Figure 10 shows the univariate logistic regressions. When CM were compared to HS, CID depression (OR = 1.08; 95% CI = 1.04–1.25; p = 0.004), CID anxiety (OR = 1.19; 95% CI = 1.02–1.37; p = 0.019), mental pain (OR = 1.40; 95% CI = 1.14–1.72; p = 0.001), PSI psychological distress (OR = 1.22; 95% CI = 1.11–1.35; p < 0.001), and PSI stress (OR = 1.18; 95% CI = 1.02–1.38; p = 0.028) were found to be statistically significant risk factors for being CM if compared to HS. On the other hand, ES Well-being (OR = 0.64; 95% CI = 0.50–0.82; p < 0.001), PSI psychological well-being (OR = 0.71; 95% CI = 0.55–0.93; p = 0.013), and PSI quality of life (OR = 0.53; 95% CI = 0.35–0.80; p = 0.003) were found to be statistically significant psychological protective factors for being CM as compared to HS (Figure 10).

Figure 10. Univariate Logistic regressions for chronic migraine subjects as compared to healthy subjects adjusted for lifetime history of psychiatric disorders, daily use of pharmacological, daily use of alcoholic beverages, daily cigarette smoking (n = 200)



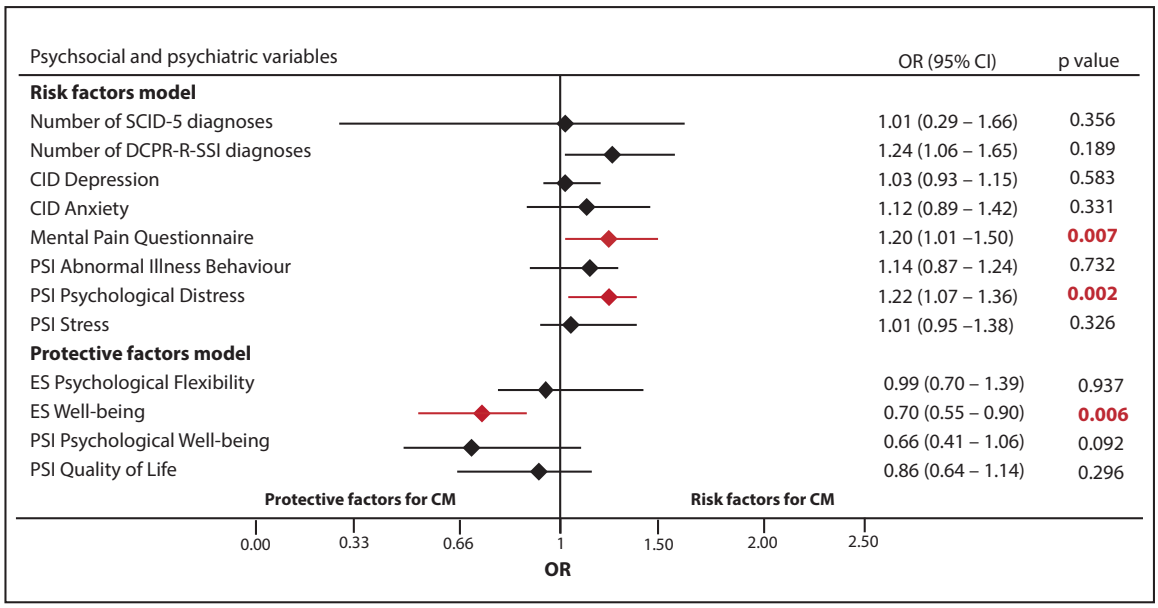
SCID-5: Structured Clinical Interview for DSM-5 disorders; DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID Depression: Clinical Interview for Depression total score depressive symptoms; CID Anxiety: Clinical Interview for Depression total score anxiety; ES: Euthymia Scale; PSI: PsychoSocial-Index; CM: chronic migraine

5.3.10.3 Multivariate Model of Risk Factors for Chronic Migraine as compared to Healthy Subjects

Figure 11 shows multivariate model of risk factors for chronic migraine as compared to healthy subjects. Mental pain (OR = 1.20; 95% CI = 1.01–1.50; p = 0.007), and psychological distress (OR = 1.22; 95% CI = 1.07–1.36; p = 0.002) were found as statistically significant risk factors for chronic migraine as compared to healthy subjects (Figure 11). Homser and Lemeshow test indicated that data fit with logistic regression model (χ^2 = 9.95; df = 8; p = 0.263). The AUC under the ROC curve was found moderately accurate (AUC = 0.86) with sensitivity of 0.82 and specificity 0.80.

Figure 11 shows multivariate model of protective factors for chronic migraine as compared to healthy subjects. ES Well-being (OR = 0.70; 95% CI = 0.55–0.90; p = 0.006) was found as statistically significant protective factor for chronic migraine as compared to healthy subjects (Figure 11). Homser and Lemeshow test indicated that data fit with logistic regression model (χ^2 = 11.84; df = 8; p = 0.158). The AUC under the ROC curve was found moderately accurate (AUC = 0.81) with sensitivity of 0.77 and specificity 0.70.

Figure 11. Multivariate Logistic regressions for chronic migraine subjects as compared to healthy subjects adjusted for lifetime history of psychiatric disorders, daily use of pharmacological, daily use of alcoholic beverages, daily cigarette smoking (n = 200). Models of risk factors and protective factors



SCID-5: Structured Clinical Interview for DSM-5 disorders; DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID Depression: Clinical Interview for Depression total score depressive symptoms; CID Anxiety: Clinical Interview for Depression total score anxiety; ES: Euthymia Scale; PSI: PsychoSocial-Index; CM: chronic migraine

5.4 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects

5.4.1 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects: Descriptive Statistics

Table 32 presents comparisons of sociodemographic characteristics. No statistically significant differences were observed between EM and CM concerning marital status, education, and employment.

Table 32. Comparison between chronic migraine subjects and episodic migraine subjects (n = 200). Sociodemographic characteristics. Chi-squared test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**		
Marital status	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Unmarried	23 (23.0)	28 (28.0)		
Married	52 (52.0)	49 (49.0)		
Cohabitant	16 (16.0)	10 (10.0)		
Separated	6 (6.0)	9 (9.0)	3.90 (5)	0.564
Divorced	1 (1.0)	3 (3.0)		
Widow/er	2 (2.0)	1 (1.0)		
Total	100 (100.0)	100 (100.0)		
Educational level	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Primary school	0 (0.0)	2 (2.0)		
Secondary school	19 (19.0)	21 (21.0)		
High school	62 (62.0)	50 (50.0)	4.95 (4)	0.292
Bachelor or master degree	17 (17.0)	23 (23.0)		
Ph.D./post-graduate	2 (2.0)	4 (4.0)		
Total	100 (100.0)	100 (100.0)		
Employment	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Worker or subordinate	15 (15.0)	14 (14.0)		
Employee	52 (52.0)	47 (47.0)		
Self-employed	6 (6.0)	2 (2.0)		
Freelance	6 (6.0)	5 (5.0)		
Manager/executive	0 (0.0)	4 (4.0)	10.65 (7)	0.293
Retired	3 (3.0)	2 (2.0)		
Student	10 (10.0)	8 (8.0)		
Unemployed	8 (8.0)	18 (18.0)		
Total	100 (100.0)	100 (100.0)		

Table 33 shows comparisons concerning anamnestic data. Statistically significant differences were found between EM and CM in lifetime psychiatric disorders (p = 0.012), daily use of pharmacological treatment (p = 0.014), and lifetime psychotherapy treatments (p = 0.027) (Table 33).

Table 33. Comparison between episodic migraine subjects and chronic migraine subjects (n = 200). Anamnestic data. Chi-squared test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**		
Anamnestic data	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Past hospitalizations	76 (76.0)	81 (81.0)	0.741 (1)	0.389
Comorbidity with other medical disorders	32 (32.0)	41 (41.0)	1.747 (1)	0.186
Food/drug allergies	30 (30.0)	20 (20.0)	2.667 (1)	0.102
Lifetime psychiatric disorders	20 (20.0)	36 (36.0)	6.349 (1)	**0.012**
Daily use of pharmacological treatments	66 (66.0)	79 (79.0)	6.004 (1)	**0.014**
Daily alcohol consumption	34 (34.0)	26 (26.0)	2.804 (1)	0.094
Daily cigarette smoking	17 (17.0)	23 (23.0)	1.125 (1)	0.289
Substance abuse	1 (1.0)	5 (5.0)	2.749 (1)	0.097
Daily coffee consumption	85 (85.0)	75 (75.0)	3.125 (1)	0.077
Lifetime psychotherapy treatment	7 (7.0)	11 (11.0)	4.916 (1)	**0.027**
Current psychotherapy treatment	25 (25.0)	27 (27.0)	0.104 (1)	0.747

5.4.2 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects: ID Migraine and Migraine Disability Assessment Questionnaire

Table 34 reports the comparisons of migraine features measured with the ID Migraine. Presence of disability due to migraine was statistically significant and more frequent in CM compared to EM (p = 0.047) (Table 34).

Table 34. ID Migraine. Difference between chronic migraine subjects and episodic migraine subjects (n = 200). Chi-squared test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**		
ID Migraine	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Presence of migraine	100 (100.0)	100 (100.0)	0.000 (1)	1.000
Presence of photophobia	67 (67.0)	60 (60.0)	1.057 (1)	0.304
Presence of nausea	76 (76.0)	77 (77.0)	0.028 (1)	0.868
Presence disability	70 (70.0)	82 (82.0)	3.947 (1)	**0.047**

Table 35 shows the comparison of levels of disability assessed via the MIDAS. Statistically significant differences were observed for grade I (minimal disability) and grade IV (severe disability). EM reported higher frequencies in minimal disability, whereas CM showed higher frequencies in severe disability (Table 35).

Table 35. Migraine disability assessment questionnaire. Difference between episodic migraine subjects and chronic migraine subjects (n = 200). Chi-squared test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**		
MIDAS	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Grade I: Minimal disability	59 (59.0)	23 (23.0)	26.788 (1)	**0.000**
Grade II: Mild disability	17 (17.0)	17 (17.0)	0.000 (1)	1.000
Grade III: Moderate disability	16 (17.0)	17 (17.0)	0.849 (1)	0.849
Grade IV: Severe disability	8 (8.0)	43 (43.0)	32.241 (1)	**0.000**

MIDAS: Migraine disability assessment questionnaire

5.4.3 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects: Brief Pain Inventory

Table 36 presents comparisons concerning pain severity and pain interference assessed with the Brief Pain Inventory. Statistically significant differences between EM and CM were reported in pain severity (p = 0.000), activity interference (p = 0.000), and affect interference (p = 0.010) (Table 36). The higher levels of BPI scores were observed in CM (Table 36).

Table 36. Brief Pain Inventory. Difference between chronic migraine subjects and episodic migraine subjects (n = 200). Mann–Whitney *U* test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**	
Brief Pain Inventory	**M (±SD)**	**M (±SD)**	**p**
Pain severity	18.28 (7.51)	23.11 (10.41)	**0.023**
Activity interference	7.23 (7.37)	11.22 (9.06)	**0.033**
Affect interference	8.40 (7.78)	13.21 (9.19)	**0.017**

5.4.4 Comparison between episodic migraine subjects and chronic migraine subjects: SCID-5 diagnoses

Table 37 reports the comparison of SCID-5 diagnoses. Overall, a higher percentage of diagnoses were observed in CM (37%) than in EM (26%) (Table 37). Among EMs, 3% showed comorbidity for one or more SCID-5 disorders, whereas among CMs, 9% showed comorbidity for one or more SCID-5 disorders (Table 37). No statistically significant difference between CM and EM were found for DSM-5 diagnoses (Table 37).

Table 37. Frequencies of SCID-5 diagnoses. Difference between episodic migraine subjects and chronic migraine subjects (n = 200). Chi-squared test; Kruskal–Wallis test

	Episodic Migraine (n = 100)	**Chronic Migraine (n = 100)**		
SCID-5	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Agoraphobia	8 (8.0)	7 (7.0)	0.072 (1)	0.788
Social Anxiety Disorder	1 (1.0)	3 (3.0)	1.020 (1)	0.312
Panic Disorder	5 (5.0)	6 (6.0)	0.096 (1)	0.756
Specific Phobia	1 (1.0)	2 (2.0)	0.338 (1)	0.561
Generalized Anxiety Disorder	0 (0.0)	2 (2.0)	2.020 (1)	0.155
Major Depressive Disorder	6 (6.0)	10 (10.0)	1.087 (1)	0.297
Persistent Depressive Disorder	0 (0.0)	2 (2.0)	2.020 (1)	0.155
Obsessive-Compulsive Disorder	2 (2.0)	1 (1.0)	0.338 (1)	0.561
Posttraumatic Stress Disorder	0 (0.0)	2 (2.0)	2.020 (1)	0.155
Body Dysmorphic Disorder	1 (1.0)	1 (1.0)	0.000 (1)	1.000
Illness Anxiety Disorder	1 (0.0)	0 (0.0)	1.005 (1)	0.316
Bipolar Disorder	1 (0.0)	1 (0.0)	0.000 (1)	1.000
Total number of SCID-5 diagnoses	26 (26.0)	37 (37.0)	3.426 (1)	0.064
SCID-5 comorbidity	**n (%)**	**n (%)**	-	**p**
1 SCID-5 diagnosis	18 (18.0)	17 (17.0)		
2 SCID-5 diagnoses	1 (1.0)	8 (8.0)		0.223
3 SCID-5 diagnoses	2 (2.0)	1 (1.0)		

SCID-5: Structured Clinical Interview for DSM-5 disorders

5.4.5 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects. DCPR-R- ISS Diagnoses

Table 38 shows the comparison of DCPR-R-ISS diagnoses. Overall, EM (90%) and CM (83%) showed a similar percentage of diagnoses (Table 38). Similarly, 27% of EM and 27% of CM showed comorbidity with one or more DCPR-R-ISS diagnoses (Table 38). EM showed statistically significant higher rates of persistent somatization ($p = 0.048$) and conversion symptoms ($p = 0.030$) (Table 38). On the contrary, CM showed a statistically significant higher percentage of irritable mood ($p = 0.022$) (Table 38).

Table 38. Frequencies of DCPR-R-SSI diagnoses. Difference between episodic migraine subjects and chronic migraine subjects (n = 200). Chi-squared test; Kruskal–Wallis test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**		
DCPR-R-SSI	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Allostatic Overload	24 (24.0)	31 (31.0)	1.229 (1)	0.268
Health Anxiety	5 (5.0)	1 (1.0)	2.749 (1)	0.097
Disease Phobia	1 (1.0)	2 (2.0)	0.338 (1)	0.561
Hypochondriasis	2 (2.0)	3 (3.0)	0.205 (1)	0.651
Thanatophobia	2 (2.0)	2 (2.0)	0.000 (1)	1.000
Illness Denial	7 (7.0)	6 (6.0)	0.082 (1)	0.774
Persistent Somatization	7 (7.0)	1 (1.0)	3.901 (1)	**0.048**
Conversion Symptoms	7 (7.0)	1 (1.0)	4.688 (1)	**0.030**
Anniversary Reaction	5 (5.0)	3 (3.0)	0.521 (1)	0.470
Demoralization	5 (5.0)	11 (11.0)	2.446 (1)	0.118
Irritable Mood	4 (4.0)	13 (13.0)	5.207 (1)	**0.022**
Type A Behavior	13 (13.0)	8 (8.0)	1.330 (1)	0.249
Alexithymia	10 (10.0)	5 (5.0)	1.802 (1)	0.179
Total number of DCPR-R-ISS diagnoses	90 (90.0)	83 (83.0)	2.089 (1)	0.147
DCPR-R-SSI comorbidity	**n (%)**	**n (%)**	-	**p**
1 DCPR-R-SSI diagnosis	26 (26.0)	37 (37.0)		
2 DCPR-R-SSI diagnoses	20 (20.0)	16 (16.0)		
3 DCPR-R-SSI diagnoses	5 (5.0)	7 (7.0)		0.425
4 DCPR-R-SSI diagnoses	1 (1.0)	1 (1.0)		
5 DCPR-R-SSI diagnoses	1 (1.0)	1 (1.0)		

DCPR-R-SSI: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview

5.4.6 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects: Clinical Interview for Depression

Table 39 shows the results of the CID. Overall, CM had higher mean item and subscale scores than EM. The differences were statistically significant for: pessimism and hopelessness ($p = 0.011$); suicidal tendencies ($p = 0.008$); work and interests ($p = 0.004$); energy and fatigue ($p = 0.006$); anxiety psychic, generalized ($p = 0.017$); anxiety somatic ($p = 0.012$); anorexia ($p = 0.031$); initial insomnia ($p = 0.011$); total score depressive symptoms ($p = 0.007$) (Table 39).

Table 39. Clinical Interview for Depression. Difference between episodic migraine subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**	
Clinical Interview for Depression	**M (±SD)**	**M (±SD)**	**p**
Feelings of depressed mood	1.80 (1.14)	2.00 (1.12)	0.124
Guilt, lowered self-esteem, and worthlessness	1.70 (1.15)	2.02 (1.30)	0.066
Pessimism and hopelessness	1.30 (0.83)	1.64 (1.20)	**0.011**
Suicidal tendencies	1.14 (0.59)	1.38 (0.88)	**0.008**
Work and interests	1.39 (0.87)	1.79 (1.15)	**0.004**
Energy and fatigue	1.84 (1.07)	2.37 (1.36)	**0.006**
Anxiety psychic, generalized	1.77 (1.11)	2.17 (1.26)	**0.017**
Panic attacks	1.05 (0.30)	1.06 (0.42)	0.734
Phobic anxiety	1.72 (1.19)	1.72 (1.14)	0.904
Avoidance, main phobia	1.71 (1.46)	1.67 (1.36)	0.957
Anxiety somatic	1.31 (0.69)	1.89 (1.50)	**0.012**
Anorexia	1.17 (0.55)	1.29 (0.62)	**0.031**
Increased appetite	1.17 (0.53)	1.24 (0.67)	0.503
Irritability	1.35 (0.61)	1.41 (0.79)	0.985
Initial insomnia	1.41 (0.87)	1.86 (1.33)	**0.011**
Delayed insomnia	1.67 (1.17)	1.86 (1.38)	0.276
Hostility	1.02 (0.20)	1.05 (0.41)	0.979
Retardation	1.10 (0.33)	1.16 (0.49)	0.464
Agitation	1.07 (0.29)	1.12 (0.41)	0.316
Depressed appearance	1.17 (0.51)	1.27 (0.65)	0.222
Total score depressive symptoms	21.55 (6.19)	24.29 (7.48)	**0.007**
Total score anxiety	6.25 (2.96)	6.62 (3.04)	0.249

5.4.7 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects. Mental Pain Questionnaire

Table 40 reports the results of the MPQ. CM showed a statistically significant higher MPQ mean score than EM (p = 0.000) (Table 40).

Table 40. Mental Pain Questionnaire. Difference between episodic migraine subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**	
	M (±SD)	**M (±SD)**	**p**
Mental Pain Questionnaire	1.05 (1.55)	2.44 (2.46)	**0.000**

5.4.8 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects: Euthymia Scale

Table 41 shows the results of the ES. CM had a statistically significant lower psychological flexibility than episodic EM (p = 0.000) (Table 41).

Table 41. Euthymia Scale. Difference between episodic migraine subjects and chronic migraine subjects (n = 200). Mann–Whitney *U* test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**	
Euthymia Scale	**M (±SD)**	**M (±SD)**	**p**
Psychological Flexibility	4.01 (1.02)	3.84 (1.03)	0.211
Psychological Well-being	3.33 (1.33)	2.57 (1.50)	**0.000**

5.4.9 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects: PsychoSocial Index

Table 42 presents the results of the PsychoSocial Index. CM showed statistically significant higher levels of psychological distress (p = 0.000) and abnormal illness behaviour (p = 0.023) than EM (Table 42). CM showed statistically significant lower levels of quality of life (p = 0.030) and psychosocial well-being (p = 0.008) than EM (p = 0.009) (Table 42).

Table 42. PsychoSocial Index. Difference between episodic migraine subjects and chronic migraine (n = 200). Mann–Whitney *U* test

	Episodic migraine (n = 100)	**Chronic migraine (n = 100)**	
PsychoSocial Index	**M (±SD)**	**M (±SD)**	**p**
Well-being	4.98 (1.09)	4.49 (1.32)	**0.008**
Stress	2.15 (1.74)	2.49 (2.05)	0.337
Psychological Distress	7.30 (4.35)	10.70 (6.70)	**0.000**
Abnormal Illness Behaviour	0.35 (0.70)	0.60 (0.91)	**0.023**
Quality of Life	2.67 (0.64)	2.44 (0.91)	**0.030**

5.4.10 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects. Univariate and Multivariate Logistic Regressions

5.4.10.1 Skewness and Kurtosis of Anamnestic, Psychosocial and Psychiatric Variables

Table 43 reports the values of skewness and kurtosis for the anamnestic data (i.e., lifetime psychiatric disorders, daily use of pharmacological treatments, lifetime psychotherapy treatment). The values of skewness and kurtosis were found to be in the range of acceptability, thus they were included in both univariate and multivariate logistic regression models as correction variables.

Table 44 showed the values of skewness and kurtosis for psychiatric and psychosocial rating scales (i.e., number of SCID-5 diagnoses; number of DCPR-R-ISS diagnoses; CID depressive symptoms; CID anxiety; Mental Pain Questionnaire; ES psychological flexibility; ES psychological well-being; PSI well-being; PSI stress; PSI psychological distress; PSI abnormal illness behaviour; PSI quality of life). All the rating scale scores showed value in the range of acceptability, thus they were selected for univariate and multivariate logistic regression analyses.

Table 43. Comparison between episodic migraine subjects and chronic migraine subjects (n = 200). Anamnestic data. Skewness and kurtosis

	Total (n =200)		**Episodic migraine (n = 100)**		**Chronic migraine (n = 100)**	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Lifetime psychiatric disorders	0.99	-1.04	1.53	0.32	0.59	-1.68
Daily use of pharmacological treatments	1.10	-0.80	1.17	-0.68	1.05	-0.91
Lifetime psychotherapy treatment	-1.10	-0.98	-0.69	-1.56	-1.14	0.09

Table 44. Comparison between episodic migraine subjects and chronic migraine subjects (n = 200). Psychosocial and psychiatric variables. Skewness and kurtosis

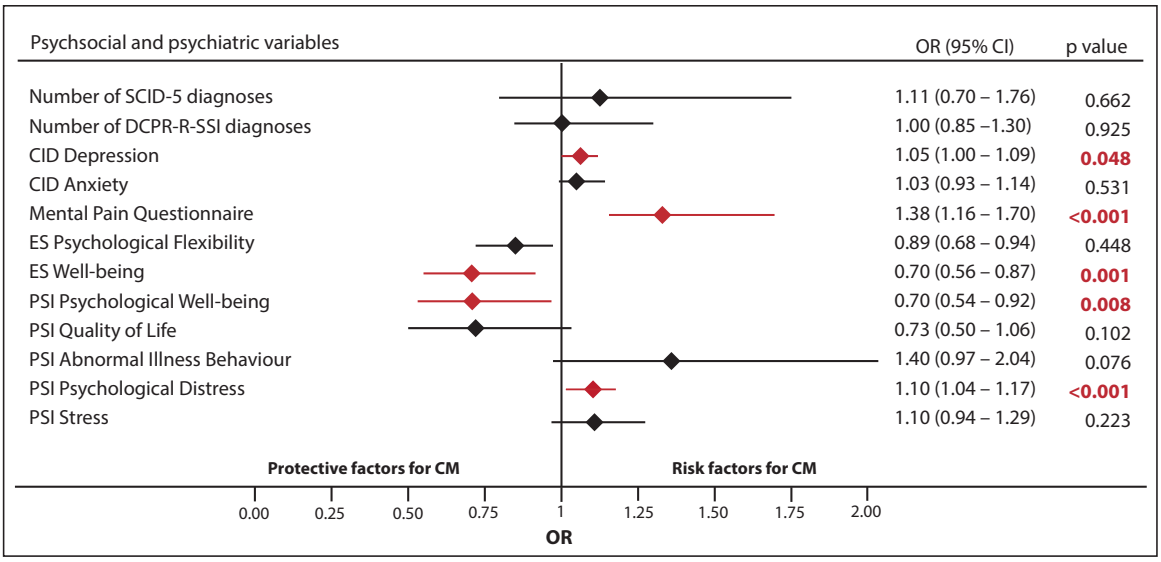
	Total (n =200)		Episodic migraine (n = 100)		Chronic migraine (n = 100)	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Number of SCID-5 diagnoses	2.25	2.02	2.86	2.02	1.83	2.86
Number of DCPR-R-ISS diagnoses	1.70	1.43	1.19	1.45	1.18	1.58
CID total score depressive symptoms	1.16	1.06	1.58	2.50	0.85	-0.04
CID total score anxiety	1.60	2.60	1.64	2.45	1.57	2.90
Mental Pain Questionnaire	1.45	1.81	1.79	2.00	-0.65	-0.47
ES Psychological Flexibility	-0.75	-0.08	-0.83	0.48	-0.68	-0.18
ES Psychological Well-being	-0.41	-0.71	-0.65	-0.26	-015	-0.87
PSI Well-being	-0.82	0.108	-1.10	-0.57	1.16	-0.44
PSI Stress	0.74	-0.11	0.66	-0.33	0.73	-0.20
PSI Psychological Distress	0.98	1.09	0.94	0.78	0.65	0.32
PSI Abnormal Illness Behaviour	1.90	2.57	2.07	2.73	1.70	2.90
PSI Quality of Life	-0.48	0.33	-0.78	0.68	-0.18	-0.10

SCID-5: Structured Clinical Interview for DSM-5 disorders. DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID: Clinical Interview for Depression; ES: Euthymia Scale; PSI: PsychoSocial-Index.

5.4.10.2 Univariate Models of Protective and Risk Factors for Chronic Migraine as Compared to Episodic Migraine

Figure 12 shows univariate logistic regressions. When CM were compared to EM, CID depression (OR = 1.05; 95% CI = 1.00–1.09; p = 0.048), mental pain (OR = 1.38; 95% CI = 1.16–1.70; p < 0.001), and PSI psychological distress (OR = 1.10; 95% CI = 1.04–1.17; p < 0.001) were found to be statistically significant risk factors for CM, whereas ES well-being (OR = 0.70; 95% CI = 0.56–0.87; p = 0.001) and PSI well-being (OR = 0.70; 95% CI = 0.54–0.92; p = 0.008) were found to be statistically significant protective factors for CM.

Figure 12. Univariate Logistic regressions for chronic migraine subjects as compared to episodic migraine subjects adjusted for daily use of pharmacological, lifetime history of psychiatric disorders, lifetime psychotherapy treatment (n = 200)



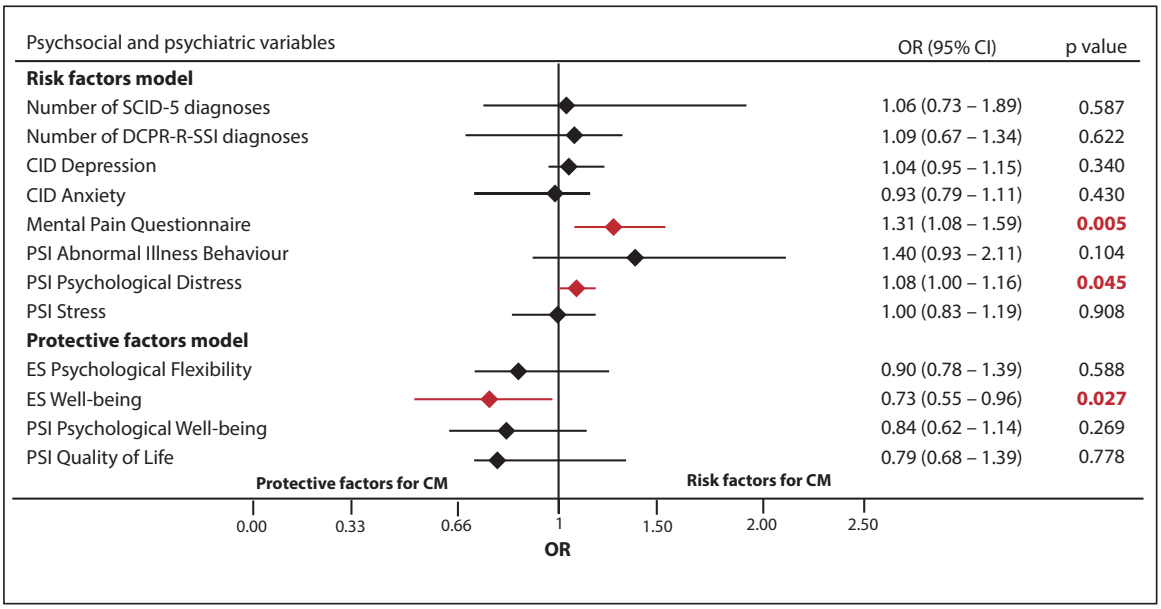
SCID-5: Structured Clinical Interview for DSM-5 disorders; DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID Depression: Clinical Interview for Depression total score depressive symptoms; CID Anxiety: Clinical Interview for Depression total score anxiety; ES: Euthymia Scale; PSI: PsychoSocial-Index; CM: chronic migraine

5.4.10.3 Multivariate Modes of Protective and Risk Factors for Chronic Migraine as Compared to Episodic Migraine

Figure 13 shows multivariate model for risk factors for being CM as compared to EM. Mental pain (OR = 1.31; 95% CI = 1.08–1.59; p < 0.001) and PSI psychological distress (OR = 1.08; 95% CI = 1.00–1.16; p = 0.045) were found as risk factors for EM as compared to CM (Figure 13). Homser and Lemeshow test (χ^2 = 4.68; df = 8; p = 0.795) indicated that data fit with logistic regression model. The AUC under the ROC curve was found moderately accurate (AUC = 0.70) with sensitivity of 0.60 and specificity 0.71.

Figure 13 shows multivariate model of protective factors for CM as compared to EM. ES psychological well-being (OR = 0.73; 95% CI = 0.55–0.96; p = 0.027) was found as statistically significant protective factor (Figure 13). Homser and Lemeshow test (χ^2 = 8.92; df = 8; p = 0.390) indicated that data fit with logistic regression model. The AUC under the ROC curve was found moderately accurate (AUC = 0.70) with sensitivity 0.70 and specificity 0.60.

Figure 13. Multivariate Logistic regression for chronic migraine subjects as compared to episodic migraine adjusted for lifetime history of psychiatric disorders, daily use of pharmacological, daily use of alcoholic beverages, daily smoking (n = 200). Models of risk factors and protective factors



SCID-5: Structured Clinical Interview for DSM-5 disorders; DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID Depression: Clinical Interview for Depression total score depressive symptoms; CID Anxiety: Clinical Interview for Depression total score anxiety; ES: Euthymia Scale; PSI: PsychoSocial-Index; CM: chronic migraine

5.5 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain

5.5.1 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: Descriptive Statistics

According to the MPQ scores (i.e., MPQ total score ≥ 3), fifty-four migraine subjects (27.0%) were classified with mental pain and 146 subjects (73.0%) were classified without mental pain. Table 45 and 46 show comparisons of sociodemographic characteristics. Migraine subjects with mental pain and migraine subjects without mental pain showed no statistically significant difference in terms of age (Table 45) and sex (Table 46). Statistically significant differences were observed in terms of educational level ($p = 0.016$) and migraine severity ($p = 0.000$). Migraine subjects with mental pain showed a lower educational level with a higher percentage of secondary school certificates, and a lower percentage of bachelor's or master's degrees. Migraine subjects with mental pain showed a statistically significant higher rate for the status of chronic migraine (75.9%) than migraine subject without mental pain (24.1%) (Table 46).

Table 45. Comparison between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Mean age. Mann–Whitney *U* test

	No mental pain (n = 146)	**Mental pain (n = 54)**	
	M (±SD)	**M (±SD)**	**p**
Age	42.11 (11.39)	43.54 (12.39)	0.306

Table 46. Comparison between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Sociodemographic characteristics. Chi-squared test

	No mental pain (n = 146)	**Mental pain (n = 54)**		
Sex	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Male	116 (79.5)	44 (81.5)		
Female	30 (20.5)	10 (18.5)	0.101 (1)	0.750
Total	146 (100.0)	54 (100.0)		
Migraine severity	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Episodic migraine	87 (59.6)	13 (24.1)		
Chronic migraine	59 (40.4)	41 (75.9)	19.888 (1)	**0.000**
Total	146 (100.0)	54 (100.0)		
Marital status	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Unmarried	36 (24.7)	15 (27.8)		
Married	71 (48.6)	30 (55.6)		
Cohabitant	22 (15.1)	4 (7.4)		
Separated	12 (8.2)	3 (5.6)	2.747 (5)	0.739
Divorced	3 (2.1)	1 (1.9)		
Widow/er	2 (1.4)	1 (1.9)		
Total	146 (100.0)	54 (100.0)		
Educational level	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Primary school	1 (0.7)	1 (1.9)		
Secondary school	23 (15.8)	17 (31.5)		
High school	85 (58.2)	27 (56.0)	8.207 (4)	**0.018**
Bachelor or master degree	32 (21.9)	8 (14.8)		
Ph.D./post-graduate	5 (3.4)	1 (1.9)		
Total	146 (100.0)	54 (100.0)		
Employment	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Worker or subordinate	18 (12.3)	11(20.4)		
Employee	77 (52.7)	22 (40.7)		
Self-employed	8 (5.5)	0 (0.0)		
Freelance	11 (7.5)	0 (11.0)		
Manger/executive	4 (2.7)	0 (0.0)	3.786 (7)	0.664
Retired	1 (0.7)	4 (7.4)		
Student	12 (8.2)	6 (11.1)		
Unemployed	15 (10.3)	11 (20.4)		
Total	146 (100.0)	54 (100.0)		

Table 47 shows comparisons of anamnestic data. Statistically significant differences were observed in lifetime psychiatric disorders (p = 0.000), daily cigarette smoking (p = 0.038), and current psychotherapy treatment (Table 47). Migraine subjects with mental pain showed a higher percentage of lifetime psychiatric disorders (p = 0.000), a higher percentage of smokers (p = 0.038) than subjects without mental pain (Table 47). Moreover, a higher percentage of migraine subjects with mental pain underwent a psychotherapy treatment at the time of the interview (p = 0.008) (Table 47).

Table 47. Comparison between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Anamnestic data. Chi-squared test

	No mental pain (n = 146)	**Mental pain (n = 54)**		
Anamnestic data	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Past hospitalizations	114 (78.1)	43 (79.6)	0.056 (1)	0.813
Comorbidity with other medical disorders	52 (35.6)	23 (42.6)	0.819 (1)	0.366
Food/drug allergies	110 (75.3)	40 (74.1)	1.624 (1)	0.854
Lifetime psychiatric disorders	31 (21.1)	25 (46.3)	12.238 (1)	**0.000**
Daily use of pharmacological treatments	102 (69.9)	43 (79.6)	1.886 (1)	0.170
Daily alcohol consumption	49 (33.6)	14 (25.9)	1.065 (1)	0.302
Daily cigarette smoking	24 (16.4)	16 (29.6)	4.287 (1)	**0.038**
Substance abuse	4 (2.7)	2 (3.7)	2.068 (1)	0.150
Daily coffee consumption	120 (82.2)	40 (74.1)	1.624 (1)	0.203
Lifetime psychotherapy treatment	34 (23.3)	18 (33.3)	2.068 (1)	0.150
Current psychotherapy treatment	6 (4.1)	8 (14.8)	6.939 (1)	**0.008**

5.5.2 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: ID Migraine and Migraine Disability Assessment Questionnaire

Table 48 reports migraine features measured evaluated via the ID Migraine. No statistically significant differences were observed in terms of the presence of migraine, presence of nausea, photophobia, and disability (Table 45).

Table 48. ID Migraine. Difference between subjects with mental pain and subjects without mental pain (n = 200). Chi-squared test

	No mental pain (n = 146)	**Mental pain (n = 54)**		
ID Migraine	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Presence of migraine	146 (100.0)	54 (100.0)	-	-
Presence of nausea	92 (63.0)	35 (64.8)	0.055 (1)	0.814
Presence of photophobia	112 (76.7)	41 (75.9)	0.014 (1)	0.907
Presence disability	108 (74.0)	44 (81.5)	1.219 (1)	0.270

Table 49 shows the levels of disability assessed via the MIDAS. Migraine subjects with mental pain reported a higher frequency of moderate and severe disability due to migraine (Table 49). These differences were statistically significant (Table 49).

Table 49. Migraine Disability Assessment Questionnaire. Difference between subjects with mental pain and subjects without mental pain (n = 200). Chi-squared test

	No mental pain (n = 146)	**Mental pain (n = 54)**		
MIDAS	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Grade I: Minimal disability	71 (48.6)	11 (20.4)	13.014 (1)	0.000
Grade II: Mild disability	29 (19.9)	5 (9.3)	3.141 (1)	0.076
Grade III: Moderate disability	19 (13.0)	14 (25.9)	4.770 (1)	**0.029**
Grade IV: Severe disability	27 (18.5)	24 (44.4)	13.975 (1)	**0.000**

MIDAS: Migraine disability assessment questionnaire

5.5.3 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: Brief Pain Inventory

Table 50 reports pain severity and pain interference assessed with the BPI. Migraine subjects with and without mental pain did not differ significantly in the severity of pain or activity interference (Table 50). On the opposite, a statistically significant difference was found in affect interference (p = 0.042) (Table 50). Migraine subjects with mental pain showed a higher level of interference in affective activities than migraine subjects without mental pain (Table 50).

Table 50. Brief Pain Inventory. Difference between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Mann–Whitney *U* test

	No mental pain (n = 146)	**Mental pain (n = 54)**	
Brief Pain Inventory	**M (±SD)**	**M (±SD)**	**p**
Pain severity	20.76 (8.95)	22.81 (11.00)	0.387
Activity interference	10.07 (8.44)	14.17 (9.42)	0.072
Affect interference	8.46 (7.56)	12.28 (9.86)	**0.042**

5.5.4 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: SCID-5 Diagnoses

Table 51 reports the comparison of SCID-5 diagnoses. Overall, migraine subjects with mental pain showed a statistically significant higher percentage of SCID diagnoses (57.4%) than migraine subjects without mental pain (20.7%) ($p = 0.000$) (Table 51). The level of comorbidity was found to be statistically significant higher in migraine subjects with mental pain (16.7%) than in those without mental pain (2.1%) ($p = 0.002$) (Table 51). Moreover, the mental pain migraine subjects showed higher rates in all DSM-5 mental disorders (Table 51). Statistically significant differences were observed in the diagnosis of: generalized anxiety disorder ($p = 0.019$); major depressive disorder ($p = 0.006$); persistent depressive disorder ($p = 0.019$); post-traumatic stress disorder ($p = 0.019$); bipolar disorder ($p = 0.019$) (Table 51).

Table 51. Frequencies of SCID-5 diagnoses. Difference between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Chi-squared test; Kruskal–Wallis test

	No mental pain (n = 146)	**Mental pain (n = 54)**		
SCID-5	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Agoraphobia	8 (5.5)	7 (13.0)	3.182 (1)	0.074
Social Anxiety Disorder	3 (2.1)	1 (1.9)	0.008 (1)	0.927
Panic Disorder	6 (4.1)	5 (9.3)	2.011 (1)	0.156
Specific Phobia	3 (2.1)	0 (0.0)	1.126 (1)	0.289
Generalized Anxiety Disorder	0 (0.0)	2 (3.7)	5.462 (1)	**0.019**
Major Depressive Disorder	7 (4.8)	9 (16.7)	7.549 (1)	**0.006**
Persistent Depressive Disorder	0 (0.0)	2 (3.7)	5.462 (1)	**0.019**
Obsessive-Compulsive Disorder	1 (0.7)	2 (3.7)	2.431 (1)	0.199
Post-traumatic Stress Disorder	0 (0.0)	2 (3.7)	5.462 (1)	**0.019**
Body Dysmorphic Disorder	1 (0.7)	1 (1.9)	0.542 (1)	0.462
Illness Anxiety Disorder	1 (0.7)	0 (0.0)	0.372 (1)	0.542
Bipolar Disorder	0 (0.0)	2 (3.7)	5.462 (1)	**0.019**
Total number of SCID-5 diagnoses	30 (20.7)	31 (57.4)	24.955 (1)	**0.000**
SCID-5 Comorbidity	**n (%)**	**n (%)**	-	**p**
1 SCID-5 diagnosis	23 (15.8)	11 (20.4)		
2 SCID-5 diagnoses	2 (1.4)	7 (13.0)	-	**0.002**
3 SCID-5 diagnoses	1 (0.7)	2 (3.7)		

SCID-5: Structured Clinical Interview for DSM-5 disorders

5.5.5 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: DCPR-R-ISS Diagnoses

Table 52 presents the comparison of DCPR-R-ISS diagnoses. Overall, no statistically significant difference was observed in the percentage of DCPR-R diagnoses between migraine subjects with mental pain (70.4%) and migraine subjects without mental pain (80.4%) (Table 52). Comorbidity of DCPR-R diagnoses was found to be statistically significantly higher in migraine subjects with mental pain than in those without mental pain ($p = 0.004$) (Table 52). Moreover, mental pain migraine subjects showed higher percentages of DCPR-R psychosomatic disorders (Table 52). Statistically significant differences were observed in the diagnosis of: allostatic overload ($p = 0.011$); thanatophobia ($p = 0.028$); persistent somatization ($p = 0.021$); anniversary reaction ($p = 0.002$); demoralization ($p = 0.001$) (Table 52).

Table 52. Frequencies of DCPR-R-SSI diagnoses. Difference between subjects with mental pain and subjects without mental pain (n = 200). Chi-squared test. Kruskal–Wallis test

	No mental pain (n = 146)	**Mental pain (n = 54)**		
DCPR-R-SSI	**n (%)**	**n (%)**	**χ^2 (df)**	**p**
Allostatic Overload	33 (22.6)	22 (40.7)	6.505 (1)	**0.011**
Health Anxiety	5 (3.4)	1 (1.9)	0.355 (1)	0.563
Disease Phobia	3 (2.1)	0 (0.0)	1.126 (1)	0.289
Hypochondriasis	4 (2.7)	1 (1.9)	0.127 (1)	0.721
Thanatophobia	1 (0.7)	3 (5.6)	4.771 (1)	**0.029**
Illness Denial	8 (5.5)	5 (9.3)	0.927 (1)	0.366
Persistent Somatization	9 (6.2)	9 (16.7)	5.309 (1)	**0.021**
Conversion Symptoms	6 (4.1)	2 (3.7)	0.017 (1)	0.897
Anniversary Reaction	2 (1.4)	6 (11.1)	9.741 (1)	**0.002**
Demoralization	6 (4.1)	10 (18.5)	11.120 (1)	**0.001**
Irritable Mood	10 (6.8)	7 (13.0)	1.894 (1)	0.169
Type A Behavior	16 (11.0)	5 (9.3)	0.121 (1)	0.728
Alexithymia	14 (9.6)	1 (1.9)	3.402 (1)	0.065
Total number of DCPR-R-ISS diagnoses	117 (80.1)	38 (70.4)	2.156 (1)	0.142
DCPR-R-SSI Comorbidity	**n (%)**	**n (%)**	**-**	**p**
1 DCPR-R-SSI diagnosis	46 (31.5)	17 (31.5)		
2 DCPR-R-SSI diagnoses	24 (16.4)	12 (22.2)		
3 DCPR-R-SSI diagnoses	6 (4.1)	06 (11.1)		**0.004**
4 DCPR-R-SSI diagnoses	0 (0.0)	02 (3.7)		
5 DCPR-R-SSI diagnoses	1 (0.7)	01 (1.9)		

DCPR-R-SSI: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview

5.5.6 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: Clinical Interview for Depression

Table 53 shows the results of the CID. Overall, migraine subjects with mental pain had higher mean item and subscale scores (Table 53). The differences were statistically significant for: feelings of depressed mood ($p = 0.000$); guilt, lowered self-esteem, and worthlessness ($p = 0.000$); pessimism and hopelessness ($p = 0.000$); suicidal tendencies ($p = 0.000$); work and interests ($p = 0.000$); energy and fatigue ($p = 0.000$); anxiety psychic, generalized ($p = 0.000$); total score depressive symptoms ($p = 0.000$); total score anxiety ($p = 0.001$) (Table 53).

Table 53. Clinical Interview for Depression. Difference between subjects with mental pain and subjects without mental pain (n = 200). Mann–Whitney *U* test

	No mental pain (n = 146)	**Mental pain (n = 54)**	
Clinical Interview for Depression	**M (±SD)**	**M (±SD)**	**p**
Feelings of depressed mood	1.67 (0.99)	2.52 (1.25)	**0.000**
Guilt, lowered self-esteem, and worthlessness	1.57 (1.02)	2.65 (1.42)	**0.000**
Pessimism and hopelessness	1.27 (0.73)	2.00 (1.50)	**0.000**
Suicidal tendencies	1.10 (0.49)	1.69 (1.11)	**0.000**
Work and interests	1.36 (0.73)	2.20 (1.43)	**0.000**
Energy and fatigue	1.97 (1.19)	2.46 (1.34)	**0.000**
Anxiety psychic, generalized	1.79 (1.11)	2.46 (1.30)	**0.000**
Panic attacks	1.06 (0.41)	1.04 (0.19)	0.951
Phobic anxiety	1.62 (1.12)	1.98 (1.24)	0.032
Avoidance main phobia	1.62 (1.37)	1.87 (1.49)	0.093
Anxiety somatic	1.55 (1.19)	1.74 (1.22)	0.230
Anorexia	1.23 (0.60)	1.24 (0.58)	0.848
Increased appetite	1.16 (0.51)	1.33 (0.80)	0.108
Irritability	1.30 (0.58)	1.59 (0.94)	0.062
Initial insomnia	1.50 (1.02)	2.00 (1.37)	**0.022**
Delayed insomnia	1.70 (1.26)	1.94 (1.34)	0.094
Hostility	1.01 (0.20)	1.09 (0.52)	0.498
Retardation	1.13 (0.39)	1.13 (0.48)	0.796
Agitation	1.08 (0.29)	1.15 (0.49)	0.319
Depressed appearance	1.18 (0.53)	1.33 (0.70)	0.104
Total score depressive symptoms	21.25 (5.79)	27.44 (7.94)	**0.000**
Total score anxiety	6.10 (2.93)	7.35 (3.00)	**0.001**

5.5.7 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: Euthymia Scale

Table 54 shows the results of the Euthymia Scale. Migraine subjects with mental pain had lower statistically significant ES scores in both psychological flexibility (p = 0.000) and psychological well-being scores (p = 0.000) than migraine subjects without mental pain (Table 54).

Table 54. Euthymia Scale. Difference between subjects with mental pain and subjects without mental pain (n = 200). Mann–Whitney *U* test

	No mental pain (n = 146)	**Mental pain (n = 54)**	
Euthymia Scale	**M (±SD)**	**M (±SD)**	**p**
Psychological flexibility	4.08 (0.90)	3.50 (1.07)	**0.000**
Psychological well-being	3.28 (1.34)	2.05 (1.45)	**0.000**

5.5.8 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain: PsychoSocial Index

Table 55 presents the results of the PsychoSocial Index. Migraine subjects with mental pain showed statistically significant higher levels of stress (p = 0.000), psychological distress (p = 0.000), and abnormal illness behaviour (p = 0.001) than migraine subjects without mental pain (Table 55). On the opposite, they showed lower levels of well-being (p = 0.000), and quality of life (p = 0.000) than migraine subjects without mental pain (Table 55).

Table 55. PsychoSocial Index. Difference between subjects with mental pain and subjects without mental pain (n = 200). Mann–Whitney *U* test

	No mental pain (n = 146)	**Mental pain (n = 44)**	
PsychoSocial Index	**M (±SD)**	**M (±SD)**	**p**
Well-Being	2.72 (0.64)	3.80 (1.34)	**0.000**
Stress	2.04 (1.76)	3.07 (2.10)	**0.000**
Psychological Distress	7.47 (5.30)	13.13 (5.46)	**0.037**
Abnormal Illness Behaviour	0.42 (0.81)	0.63 (0.83)	**0.001**
Quality of Life	2.72 (0.64)	2.11 (0.98)	**0.000**

5.5.9 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain. Univariate and Multivariate Logistic Regressions

5.4.9.1 Skewness and Kurtosis of Anamnestic, Psychosocial, and Psychiatric Variables

Table 56 reports the values of skewness and kurtosis for the anamnestic data (i.e., educational level, lifetime psychiatric disorders, daily smoking, current psychotherapy treatment). The values of skewness and kurtosis were found to be in the range of acceptability, thus they were included in both univariate and multivariate logistic regression models as correction variables.

Table 57 showed the values of skewness and kurtosis for psychiatric and psychosocial rating scales (i.e., number of SCID-5 diagnosis; number of DCPR-R-ISS diagnosis; CID depressive symptoms; CID anxiety; ES psychological flexibility; ES psychological well-being; PSI well-being; PSI stress; PSI psychological distress; PSI abnormal illness behaviour; PSI quality of life). All the rating scales showed value in the range of acceptability, thus were selected for univariate and multivariate logistic regression analyses.

Table 56. Comparison between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Anamnestic data. Skewness and kurtosis

	Total (n =200)		No mental pain (n = 146)		Mental pain (n = 54)	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Migraine severity	0.17	-2.02	0.39	-1.87	-1.25	-0.46
Educational level	0.35	0.08	0.34	0.19	0.58	0.30
Lifetime psychiatric disorders	0.99	-1.04	1.42	0.02	0.15	-2.05
Daily cigarette smoking	1.83	1.37	1.30	1.39	1.08	1.06
Current psychotherapy treatment	2.39	2.63	2.62	2.34	2.01	2.89

Table 57. Comparison between migraine subjects with mental pain and migraine subjects without mental pain (n = 200). Psychosocial and psychiatric variables. Skewness and kurtosis

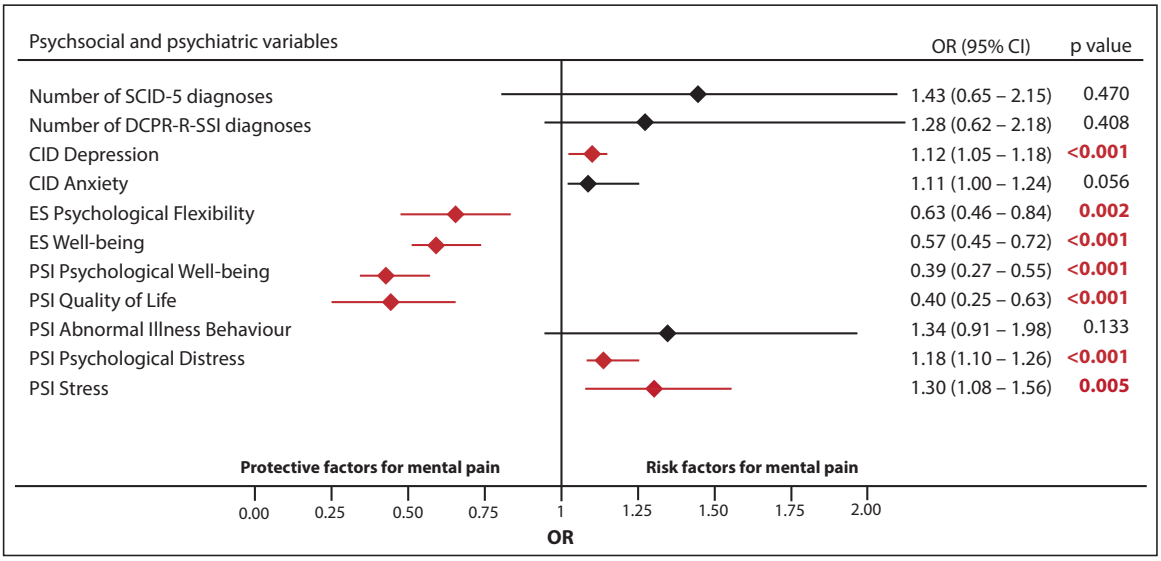
	Total (n =200)		No mental pain (n = 146)		Mental pain (n = 54)	
	Skewness	**Kurtosis**	**Skewness**	**Kurtosis**	**Skewness**	**Kurtosis**
Number of SCID-5 diagnoses	2.25	2.02	2.45	1.72	1.90	2.26
Number of DCPR-R-ISS diagnoses	1.70	1.43	1.87	1.23	1.36	1.82
CID total score depressive symptoms	1.16	1.06	1.33	1.96	0.62	-0.24
CID total score anxiety	1.60	2.60	1.99	2.28	0.84	1.51
ES Psychological Flexibility	-0.75	-0.08	-0.82	-0.10	-0.56	-0.11
ES Psychological Well-being	-0.41	-0.71	-0.58	-0.32	0.09	-0.98
PSI Well-Being	-0.82	0.11	-0.89	0.12	-0.20	-0.44
PSI Stress	0.74	-0.11	0.81	0.43	-0.01	-0.47
PSI Psychological Distress	0.98	1.09	1.55	2.93	0.31	-0.34
PSI Abnormal Illness Behaviour	1.90	2.57	2.31	2.63	1.00	-0.14
PSI Quality of Life	-0.48	0.33	-0.31	0.40	0.14	0.64

SCID-5: Structured Clinical Interview for DSM-5 disorders. DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID: Clinical Interview for Depression; ES: Euthymia Scale; PSI: PsychoSocial-Index.

5.5.9.2 Univariate Models of Protective and Risk Factors for Mental Pain in Migraine Subjects

Figure 14 shows univariate logistic regressions. When migraine subjects with mental pain were compared to migraine subjects without mental pain, CID depression (OR = 1.12; 95% CI = 1.05–1.18; p < 0.001), PSI psychological distress (OR = 1.18; 95% CI = 1.10–1.26; p < 0.001), and PSI stress (OR = 1.30; 95% CI = 1.08–1.56; p = 0.005) were found to be statistically significant risk factors for having higher levels of mental pain (Figure 14). ES psychological flexibility (OR = 0.63; 95% CI = 0.46–0.84; p = 0.002) and ES well-being (OR = 0.57; 95% CI = 0.45–0.72; p < 0.001) as well as PSI well-being (OR = 0.39; 95% CI = 0.27–0.55; p < 0.001) and PSI quality of life (OR = 0.40; 95% CI = 0.25–0.63; p < 0.001) were found to be statistically significant protective factors for having high levels of mental pain in migraine (Figure 14).

Figure 14. Univariate logistic regressions for factors for mental pain in migraine subjects as compared to in migraine subjects without mental pain, adjusted for age, sex, migraine severity, educational level, lifetime psychiatric disorders, daily smoking, and current psychotherapy treatment (n = 200)



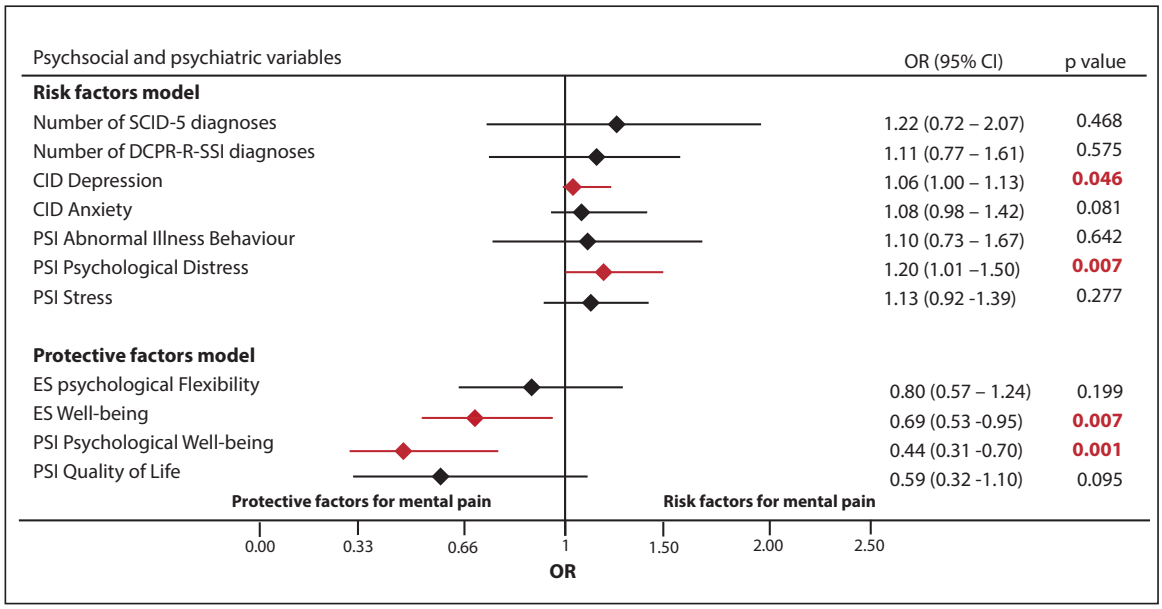
SCID-5: Structured Clinical Interview for DSM-5 disorders. DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID: Clinical Interview for Depression; ES: Euthymia Scale; PSI: PsychoSocial-Index.

5.5.9.3 Multivariate Modes of Risk and Protective Factors for Mental Pain in Migraine Subjects

Figure 15 shows multivariate model for risk factors for having high levels of mental pain in migraine patients. CID depression (OR = 1.06; 95% CI = 1.00–1.13; p = 0.046) and PSI psychological distress (OR = 1.20; 95% CI = 1.01–1.50; p = 0.007) were found as statistically significant risk factors for having high mental pain (Figure 15). Homser and Lemeshow test (χ^2 = 10.70; df = 8; p = 0.220) indicated that data fit with logistic regression model (Figure 15). The AUC under the ROC curve was found moderately accurate (AUC = 0.82) with sensitivity of 0.67 and specificity 0.91.

Figure 15 shows multivariate model of protective factors for having high mental pain in migraine subjects. ES psychological well-being (OR = 0.69; 95% CI = 0.53–0.95; p = 0.007) and PSI psychosocial well-being (OR = 0.44; 95% CI = 0.31–0.70; p = 0.001) were found as statistically significant protective factors (Figure 15). Homser and Lemeshow test (χ^2 = 11.75; df = 8; p = 0.22) indicated that data fit with logistic regression model. The AUC under the ROC curve was found moderately accurate (AUC = 0.83) with sensitivity 0.59 and specificity 0.92.

Figure 15. Multivariate Logistic regressions adjusted for age, sex, educational level, migraine severity, lifetime psychiatric disorders, daily smoking, and current psychotherapy treatment (n = 200). Models of risk and protective factors for mental pain in migraine subjects



SCID-5: Structured Clinical Interview for DSM-5 disorders. DCPR-R-ISS: Diagnostic Criteria for Psychosomatic Research-Revised Semi-Structured Interview; CID: Clinical Interview for Depression; ES: Euthymia Scale; PSI: PsychoSocial-Index.

6 Discussion

6.1 Comparison between Healthy Subjects and Episodic Migraine Subjects

EM and HS differed for food or drug allergies, daily use of pharmacological treatments, daily consumption of alcoholic beverages, and daily cigarette smoking which is consistent with the literature (Bektas, Karabulut, Doganay, & Acar, 2017; Brusa et al., 2019; Rozen, 2011; Gan, Estus, & Smith, 2016; Dueland, 2015). Bektas and colleagues found that allergies are more frequent in migraineurs, and allergens could be a trigger for migraine attacks (Bektas et al., 2017). Literature showed that episodic migraine patients are more prone to the use of multiple drugs, particularly during self-medication attempts (Brusa et al., 2019). Lower rates of alcohol consumption and smoking behaviors in episodic migraine than healthy controls are consistent with the literature since these factors are both triggers for migraine attacks (Rozen, 2011; Gan, Estus, & Smith, 2016; Dueland, 2015).
As expected, the presence of disability due to migraine and pain were found in EM and not in HS. Moreover, in episodic migraine outpatients, the levels of disability assessed via the MIDAS were more frequent in minimal, mild, and moderate grades, which is consistent with the literature (Bigal et al., 2003).

A similar percentage of SCID-5 diagnoses were observed in episodic migraine subjects and healthy subjects, although the literature suggests higher rates of mental disorders in episodic migraine patients than healthy controls (Buse et al., 2013; Minen et al., 2016). To be noted that, in the present research, the rate of SCID-5 diagnoses was relatively low both in episodic migraine and healthy subjects and this may explain the failure to achieve the statistical significance for the SCID-5 dimensions. A higher rate of generalized anxiety disorder was found in HS than EM, which is not consistent with the literature (Baskin & Smitherman, 2009). However, this difference could be explained by the fact that cognitive and behavioral symptoms of anxiety (e.g., 'intrusive thoughts about work', 'feeling under pressure', 'impatience') were found to be migraine triggers (Wacogne et al., 2003), and, in the present study, EM subjects were found to have low levels of anxiety, less severe migraine, minimal disability, and higher social functioning. Therefore, EM subjects could have learned protective behaviors and more adaptive thoughts towards the anxiety related to migraine attacks (i.e., migraine triggers). In turn, these learned behaviour and thoughts could have reduced also anxious symptoms bringing them

below the diagnostic threshold.
On the opposite, higher rates of major depressive disorder and agoraphobia were observed in EM than HS, even though, these differences were not statistically significant. These findings are in line with the literature (Radat & Swendesen, 2005).

Statistically significant higher rates of DCPR-R psychosocial syndromes were observed in episodic migraine outpatients than in healthy subjects. This finding is in line with Williams at al. who highlighted higher rates of psychosomatic symptoms in migraine patients (Williams at al., 1992). In particular, episodic migraine patients showed statistically significant higher rates of DCPR-R illness denial, in line with Demjen and Bakal that found illness denial as the most frequent psychosomatic ailment in migraine subjects (Demjen & Bakal, 1980). Moreover, episodic migraine patients showed higher rates of DCPR-R illness behaviour, conversion symptoms, persistent somatization, and anniversary reaction than healthy subjects. These finding are in accordance with Williams at al. who found difference between healthy subjects and migraine outpatients in terms of frequencies of conversion symptoms and somatization (Williams at al., 1992). Demjen and Bakal highlighted the presence of denial in migraine subjects describing a cognitive shift, whereby the patient's primary concern moves from situational and interpersonal stress to distress associated with the disorder itself (Demjen & Bakal, 1985).

No difference in terms of CID depression and CID anxiety were observed between healthy subject and episodic migraine subjects although the literature shows higher levels of depressive and anxious symptoms in episodic migraine subjects than in healthy subjects (Radat & Swendesen, 2005; Zwart et al., 2008; Baskin & Smitherman, 2009). This absence of differences could be explained by the positive effects of the received treatments that have decreased the migraine severity (Bigal et al., 2003). Similarly, healthy subjects reported higher scores in some CID dimensions (i.e., guilt, lowered self-esteem; worthlessness and loss of interest). Again, these results are not consistent with the literature (Zwart et al., 2008; Baskin & Smitherman, 2009). This inconsistency could be explained by the fact that subjects with EM showed minimal levels of disability in the social, occupational and recreational domains. These factors could have protected EM patients from loss of interest and development of a poor self-image. In fact, literature has shown that a satisfactory social life with a high number of social interactions is a protective factors for the insurgence of depressive symptoms (Nagy & Moore, 2017).
On the contrary, episodic migraine subjects showed higher levels of CID phobic anxiety and CID avoidance behaviours, in accordance with the literature (Baskin & Smitherman, 2009). Lastly, episodic migraine subjects showed higher CID retardation and lower CID agitation than controls. This result could be explained by the fact that retardation may overlap with some behavioural aspects of migraine dis-

ability (i.e., loss of mobility), and agitation could be more frequent in HS since high behavioural activation is a migraine trigger (Baskin & Smitherman, 2009).

No difference between episodic migraine and healthy subjects were observed in terms of mental pain. It could be explained by the fact that the majority of EM experienced a low level of disability due to migraine and low levels of depressive symptoms related to mental pain such as suicidality, helplessness and hopelessness (Shneidman, 1998; Orbach et al., 2003).

No differences in terms of ES flexibility and ES well-being were observed between episodic migraine and healthy subjects. Again, the high level of euthymia observed in episodic migraine group could reflect the protective effect of the received treatments as well as the low level of disability presented.

Concerning the PSI, a statistically significant difference between EM and HS was found in terms of levels of psychological distress and quality of life. EM showed higher levels of psychological distress than HS. This result is consistent with the literature showing a higher psychosocial impairment in episodic migraine patients concerning social and family activity than in the general population (Lipton et al., 2003a; Rueveni, 1992; Smith, 1998). EM subjects showed lower levels of quality of life than healthy subjects, consistently with the literature (Lipton et al., 2003a; Lipton et al., 2003c; Hamelsky, Lipton, & Stewart, 2005).

Both univariate and multivariate logistic regressions showed that higher levels of anxiety symptoms and PSI psychological distress were statistically significant risk factors of being episodic migraine subjects as compared to healthy subjects. These findings are consistent with the literature showing that anxiety symptoms are a risk factor for the occurrence of migraine in EM, even though the magnitude of the OR was found to be lower in the present study (Radat & Swendesen, 2005; Baskin & Smitherman, 2009). Similarly, psychosocial impairment was found to be related to the occurrence of episodic migraine, in particular, the effect of psychological stress due to environmental challenges was evident (Dodick, 2009; Borsook, Maleki, Becerra, & McEwen, 2012).

Both univariate and multivariate logistic regressions showed that higher levels of PSI quality of life were a protective factor for belonging to the condition of episodic migraine as compared to healthy subjects. The literature showed that a lower quality of life was a risk factor for EM (Hamelsky et al., 2005). It could be hypothesized that the other way round is true: a higher level of quality of life might reduce the risk of EM as compared to HS.

6.2 Comparison between Healthy Subjects and Chronic Migraine Subjects

CM and HS differed for comorbidity with other medical disorders, presence of lifetime psychiatric disorders, daily alcohol consumption, and daily cigarette smoking, which are consistent with the literature (McLean & Mercer 2017; Rozen, 2011; Gan, Estus, & Smith, 2016; Dueland, 2015). McLean and Mercer, in a nationally representative dataset, found that chronic migraine patients had higher rates of physical and mental comorbidities than healthy controls, showing percentages similar to the ones observed in the present study (McLean & Mercer, 2017). Lower rates of alcohol consumption and smoking behaviors were observed in CM than HS; these findings are consistent with the literature that describes these factors as migraine triggers and shows that the effects of these triggers are related to the frequency of migraine attacks with higher effects in subjects with a higher frequency of migraine attacks (Rozen, 2011; Gan, Estus, & Smith, 2016; Dueland, 2015).
As expected, HS did not show migraine symptoms and pain related to migraine attacks when they were compared to CM. Levels of disability assessed via the MIDAS showed that the higher percentage of CM presented a severe disability, which is consistent with the literature (Bigal et al., 2003).

Concerning the DSM-5 diagnoses, CM subjects had a statistically significant higher rates of major depressive disorder than HS. The rate of depressive disorders was found consistent with that observed by Zwart et al. (Zwart et al., 2003).

CM subjects showed statistically significant higher rates of DCPR-R allostatic overload than HS. This finding is consistent with the literature that described chronic stress as a migraine trigger in CM (Borsook et al., 2012; Dodick, 2009). CM showed statistically significant higher rates of DCPR-R persistent somatization in line with Maizels and Burchette who showed that functional somatic symptoms were more common in CM than in HS (Maizels & Burchette, 2004). Moreover, CM showed higher rates of illness denial than controls, in line with Demjen and Bakal (Demjen & Bakal, 1980; 1985). DCPR-R type A behaviour was found statistically significant higher in healthy controls than in CM. No data are available in literature on this issue. However, this difference could be explained by the fact that the personality profile of the type A behaviour (time urgency; free-floating/easily aroused hostility; impatience with slowness; concentrating on more than one activity at a time; self-preoccupation, a tendency to challenge and compete with others even in non-competitive situations) seems to include behaviors that encompass a large variety of migraine triggers such as high behavioral activation (Stewart et al., 2000), perception of stress (Dodick, 2009), and irritability (Peres et al., 2017). Besides, the high level of working activities endorsed by the type A behavior subjects are in

contrast with the high level of work disability commonly observed in CM (Lipton et al., 2003a). Thus, it could be hypothesized that type A behavior is not related to CM since it includes a large array of migraine triggers that does not fit with the protective behavior observed in chronic migraine patients (i.e., avoidance of behavioral and emotional activation) (Martins & Parreira, 2001).

CID anxiety and CID depression scores were higher in CM than HS, in line with the literature which showed that depressive and anxiety symptoms are more frequent in subject with CM than in the general population (e.g., Radat & Swendesen, 2005; Zwart et al., 2008; Baskin & Smitherman, 2009; Buse et al., 2012; Minen et al., 2016). CM showed higher CID scores than HS in terms of: feelings of depressed mood; guilt, lowered self-esteem, and worthlessness; pessimism and hopelessness; suicidal tendencies; energy and fatigue; phobic anxiety; anxiety somatic; anorexia; retardation; depressed appearance. These results are in line with the literature which described CM as characterized by high anxious and depressive traits (Wolf, 1937; Zwart et al., 2008; Hsu et al., 2009). Recent research indicated that this association may be explained by the activation of neuropathic mechanisms that involve limbic activation shared by both pain and affective disorders (Guidetti & Galli, 2002; Rome & Rome, 2000). Concerning the higher levels of CID hopelessness and suicidal tendencies observed in CM with the respect of HS, these findings are in accordance with literature that highlighted hopelessness (Zampieri, Tognola, & Galego, 2014) or hopelessness and suicidal tendencies as the core aspects of depressive symptoms in CM (Pompili et al., 2010). CM also showed a higher CID delayed insomnia than HS, which is consistent with the literature which reported the highest prevalence of sleep disturbances in CM than in the general population (Kelman & Rains, 2005).

CM showed higher levels of mental pain than HS. Unfortunately, there are no data available on this issue. However, the literature showed that CM is a source of great distress, with impairment of pleasure, family functioning, and working activities (e.g., Lipton et al., 2003a; Lipton et al., 2003c; Hamelsky et al., 2005). The literature also showed that the decreased quality of life in CM can result in hopelessness, despair, depression, anxiety, and suicidal attempts (e.g., Breslau, 1992; Fasmer & Oedegaard, 2001; Hung, Wang, Yang, & Liu, 2008; Breslau et al., 2012). In this framework, the term mental pain was coined to describe a psychological pain that takes hold of the mind when the hurt, anguish and emotional suffering lead to the perception of negative changes in the self, and these changes are accompanied by strong negative feelings such as guilt, fear, anxiety, loneliness, helplessness, loss of self, disconnection, and torment that are the most relevant indicators of the impairment of subjective well-being (Tossani, 2013; 2104). Thus, mental pain could represent a more accurate indicator of the acute psychological suffering experienced by CM subjects.

CM reports lower levels of ES psychological well-being than HS, which is in line with the literature (Shields & Wheatley Price, 2005). They also showed lower levels of ES psychological flexibility than HS, which is consistent with Almarzooqi et al. (Almarzooqi et al., 2017).

Concerning the PSI index, chronic migraine subjects had lower levels of PSI well-being and lower levels of PSI quality of life than HS. These findings are consistent with Wessman and colleagues (Wessman et al., 2007) and Hamelsky and colleagues (Hamelsky et al., 2005). Moreover, a higher level of psychosocial distress was founded in CMs with respect to HSs, consistently with Rueveni (Ruveni, 1992) and Smith (Smith, 1998).

Univariate logistic regressions showed that CID depression, CID Anxiety, mental pain, PSI stress and PSI psychological distress were risk factors for being CM if compared to HS. These results are consistent with the literature (e.g., Zwart et al., 2008; Blackburn-Munro & Blackburn-Munro, 2001) except for mental pain, since, there are no data concerning the relationship between CM and mental pain currently available. When the multivariate logistic regression analysis was run, psychological distress and mental pain survived as statistically significant risk factors for CM as compared to HS. The relationship between distress and chronic migraine is well-investigated, showing that higher levels of distress are associated with a higher risk of CM (e.g., Rueveni, 1992; Smith, 1998; Dodick, 2009). On the opposite, no data are available concerning the risk of being CM associated with mental pain. It could be hypothesized that mental pain is a risk factor for CM starting for the condition of HS since it encompasses several psychological dimensions that were found as risk factors for CM compared to HS such as guilt, hopelessness, and suicidal ideation (Hung, Wang, Yang, & Liu, 2008).

Univariate logistic regression analyses highlighted that higher levels of ES well-being and quality of life are protective factors for being CM as compared to HS. When multivariate logistic regression analysis was run, only ES psychological well-being survived as a protective factor for CM as compared to HS. No data are available on this issue. It could be hypothesized that the component of well-being included in the Euthymia Scale (i.e., restorative sleep, to feel cheerful, calm, active, interested in things) includes the most prominent protective factors from high-frequency migraine attacks. In fact, sleep disturbances and allostatic load are the most relevant migraine triggers (Kelman & Rains, 2005; Dodick, 2009) while the presence of restorative sleep was found to be a homeostatic or allostatic factor, enabling the organism to achieve positive mental health (Fava & Bech, 2016). Similarly, feeling cheerful, calm, and active is in opposition with irritability, anger, anxiety, and agitation that were found to be further relevant migraine triggers (Minen et al., 2016).

6.3 Comparison between Episodic Migraine Subjects and Chronic Migraine Subjects

CM and EM showed statistically significant differences concerning the presence of lifetime psychiatric disorders, daily use of pharmacological treatments, and lifetime psychotherapy treatment. These results are consistent with the literature on rates of psychiatric comorbidity (Blumenfeld et al., 2010; Buse et al., 2010), daily pharmacological medication (Pini et al., 1996; Ferrari et al., 2007), and past psychotherapy treatments (Peres et al., 2019).

When CM were compared with EM, they showed a higher rate of presence of disability measured with the ID Migraine and a higher percentage of subjects with a severe disability assessed via the MIDAS. On the opposite, EM showed higher rates of minimal disability assessed via the MIDAS than CM. These findings are consistent with Bigal and colleagues (Bigal et al., 2003).

CM showed higher levels of pain than CM in all BPI scales (i.e., pain severity; activity interference; affect interference), which is consistent with the literature that described CM subjects as more likely to experience severe pain and a higher disability than EM (Blumenfeld et al., 2011).

No statistically significant difference between CM and EM were found concerning DSM-5 diagnoses although the literature suggests higher rates of mental disorders in CM than in EM (Hamelsky & Lipton, 2006; Minen et al., 2016; McLean & Mercer, 2017). To be noted that, in the present research, the rate of SCID-5 diagnoses was relatively low both in chronic migraine and episodic migraine subjects and this may explain the failure to achieve the statistical significance. However, although not statistically significant, the rate of major depression was double in CM than in EM. The enrolment of a larger sample might probably solve such an inconsistency with the literature.

Concerning DCPR-R syndromes, allostatic overload was found more frequent in CM than in EM, even though, this difference did not achieve the statistical significance. This result is in line with the literature (Dodick, 2009). Moreover, although not statistically significant, the rate of DCPR-R demoralization was double in chronic migraine patients than in episodic migraine subjects which in line with the literature (Zwart et al., 2008). Again, the enrolment of a larger sample might probably solve this inconsistency. On the contrary, EM showed higher rates of DCPR-R persistent somatization and conversion symptoms than CM, which is not consistent with literature showing that somatic symptoms are more common in patients with chronic migraine (Maizels, 2004). This inconsistency could be explained under the light of the high frequency of illness denial observed in both EM and CM subjects. Demjen and Bakal have shown that a cognitive shift moves the attention of migraine

subjects prominently towards migraine symptoms that become the main argument to communicate psychological distress to clinicians (Demjen & Bakal, 1980). It could be hypothesized a positive relationship between the frequency of migraine attacks and the frequency of the activation of the cognitive shift. In the case of EM subjects, it could be hypothesized the presence of a weak activation of the cognitive shift that have allowed patients to report somatization and conversion symptoms to the clinician. In the case of CM, it could be hypothesized the presence of a strong activation of the cognitive shift that did not allow patients to report somatization and conversion symptoms to clinician, focusing their attention exclusively on pain and disability related to migraine. Thus, CM could give less attention to psychosomatic symptoms and they could provide less detail to the clinician concerning conversion and somatic disorder that in turn could not reached the diagnostic threshold.

CID depression total score was found higher in CM than in EM, in line with the literature (Buse et al., 2012). CM also showed higher CID scores than EM in pessimism and hopelessness, suicidal tendencies, work and interests, energy and fatigue, anxiety somatic, anorexia, and initial insomnia. Again, these results are in line with literature showing CM subjects as characterized by anxious and depressive traits (Wolf, 1937; Zwart et al., 2008; Hsu et al., 2009). Moreover, these findings are in line with studies reporting that the levels of depressive symptoms increase as headache frequency increases (e.g., Zwart et al., 2008; Buse et al., 2012) and consistent with studies on the association between suicidality and headache frequency reporting that the levels of suicidal ideation and hopelessness increases as the headache frequency increases (Lin et al., 2019).

CM showed higher levels of mental pain than EM. As previously reported, mental pain could represent a candidate for a more accurate indicator of the acute psychological suffering experienced by CM subjects also when they were compared to EM.

ES psychological well-being and ES psychological flexibility were found lower in CM than in EM, consistently with the literature which showed that the decrease in well-being levels and psychological flexibility are associated with the increase migraine severity (Almarzooqi et al., 2017; McCracken & Morley, 2014).
Psychological distress assessed via the PSI was found statistically significant higher in CM than in EM. These results are in line with other studies which reported a higher psychosocial impairment in CM as compared to EM (Meletiche et al., 2001; Ferrari et al., 2006; Buse et al., 2009; Scher, et al., 2008). PSI abnormal illness behaviour was found statistically significant higher in CM than EM. This result is consistent with previous data showing that CM sufferers compared to EM are characterized by less adaptive illness behaviors (Siniatchkin, Riabus, & Hasenbring, 1999); they are more prone to catastrophize their bodily perception (Siniatchkin, Riabus,

& Hasenbring, 1999); to adopt dysfunctional consulting behaviour (e.g., overuse or misuse of medical/care) (Edmeads et al., 1993) as well as to not follow the recommendation of physicians (Frediani, Martelletti, & Bussone, 2004). PSI psychosocial well-being and PSI quality of life were found to be lower in CM than EM, which is in line with the literature (Osterhaus et al., 1994; Meletiche et al., 2001). Previous results showed that, compared with EM, patients with CM had statistically and clinically significant lower levels of psychosocial well-being and quality of life (Osterhaus et al., 1994; Meletiche et al., 2001).

Univariate logistic analyses showed that CID depression, PSI psychological distress, and mental pain were risk factors for belonging to the CM condition as compared to EM. Results are in line with the literature which showed depression (Zwart et al., 2008) and distress (Scher er al., 2008) as risk factors for migraine chronicity. On the contrary, no data are available on mental pain. When the multivariate model of risk factors was run, only PSI psychological distress and mental pain survived as statistically significant risk factors for CM as compared to EM. These results are consistent with the literature which showed that distress is a risk factor for passing from the condition of EM to CM (Scher et al., 2008). Again, no data are currently available on mental pain, thus conclusions based on the literature cannot be drawn. The relevance of mental pain as risk factor for CM as compared to EM could be explained by the fact that mental pain includes symptoms that were highlighted also as risk factor for migraine chronicity (i.e., helplessness, hopelessness and suicidal thoughts) (De Filippis et al., 2008). It may also represent an evidence of its higher accuracy as indicator of psychological suffering in CM.

Univariate logistic regressions showed that psychosocial well-being and ES well-being represents protective factor for CM as compared to EM. When a multivariate logistic regression model was run, only the ES well-being survived. As previously stated, this result could be explained by the fact that the component of well-being, as assessed via the Euthymia Scale, encompasses factors (i.e., restorative sleep, to feel cheerful, calm, active, interested in things) which are not risk factors for migraine chronicity, such as sleep disturbances, irritability, anger, anxiety and agitation (Minen et al., 2016).

6.4 Comparison between Migraine Subjects with Mental Pain and Migraine Subjects without Mental Pain

Migraine subjects with high mental pain showed a lower educational level, a higher migraine severity as well as higher rates of lifetime psychiatric disorder, daily cigarette smoking, and previous psychotherapy treatments than migraine subjects with low mental pain. No data are available on these issues since it is the first

study that assessed mental pain in subjects with migraine. However, to be noted, migraine patients with high levels of mental pain were found to be more likely to be CM. Being a CM subjects also means having sociodemographic and anamnestic characteristics that the literature has shown to be risk factors for migraine chronicity; i.e., low education (Buse et al., 2010), cigarette smoking vs no smoking (Rozen, 2011), and poor mental health (Mc Lean & Mercer, 2017). Thus, migraine subjects with high mental pain showed less resources and adaptive behaviors to cope with migraine attacks.

Migraine subjects with high mental pain and migraine subjects with low mental pain showed no difference on ID migraine (i.e., nausea, photophobia and disability). On the other hand, migraine subjects with high mental pain reported a statistically significant higher frequency of moderate and severe disability due to migraine assessed via the MIDAS than migraine subjects with low mental pain. Again, no data are available in the literature on this issue, thus comparisons cannot be made. It could be hypothesized that emotional suffering related to the severe disability due to migraine is described by the items of the MPQ that encompasses statements as "My pain is with me all the time" or "My pain will never go away". In turn the presence of mental pain could have clustered migraine subjects with the highest level of disability.

Affect interference measured with the BPI was found statistically significant higher in migraine subjects with high mental pain than in migraine subjects with low mental pain. No previous findings are available on this issue. However, it could be hypothesized that mental pain encompassing aspects of loneliness and helplessness (e.g., "I will never find what I have lost") and it could identify those migraine subjects who are more prone to social withdrawal in response to headache attacks.

Migraine subjects with high mental pain showed statistically significant higher rates of DSM-5 diagnoses than migraine subjects with low mental pain. The most common diagnoses are: generalized anxiety disorder, major depressive disorder, persistent depressive disorder, post-traumatic stress disorder, and bipolar disorder. No previous findings are available on this issue. However, this difference can be explained by the fact that migraine subjects with high mental pain were found to have in the majority of cases a diagnosis of CM and the literature showed that CM had the highest level of psychiatric comorbidities (Minen et al., 2016).Otherwise, this difference could be explained by the fact that mental pain was found frequently associated with other mental disorders such as depressive disorder, bipolar disorder, anxiety disorder, and PTSD (Tossani, 2013); it could be hypothesized that these comorbidity is true also in migraine subjects with high levels of mental pain.

High mental pain migraine subjects showed statistically significant higher percentages of DCPR-R diagnosis of allostatic overload, demoralization, thanato-

phobia, anniversary reaction, and persistent somatization than migraine subjects with low mental pain. No data are available in the literature concerning this relationship. However, it could be hypothesized that the highest rates of allostatic overload observed in migraine subjects with high mental pain could be explained by the severe self-perception of helplessness experienced by migraine patients with high mental pain (e.g., "I cannot understand why I feel this pain"; "My life makes no sense") that could lead to have a more frequent allostatic overload in response to the environmental challenges (i.e., stressors are experienced as exceeding the individual coping skills) (Fava et al., 2019). Similarly, the higher frequency of demoralization in migraine subjects with high mental pain could be explained by the fact that mental pain encompasses hopelessness and helplessness, and by the fact that migraine subjects with high mental showed the highest level of disability due to migraine as well as less sources and adaptive behaviors to cope with migraine attacks. These characteristics seems to fit well with the clinical features of demoralization that encompasses a cluster of symptoms characterized by a feeling of subjective incompetence, impotence, isolation, and despair resulting in the inability to cope with stressors (Fava, Cosci, & Sonino, 2017).

Concerning the higher rate of thanatophobia in migraine subjects with high mental pain, it could be hypothesized that thanatophobia represents a clinical phenomenon secondary to mental pain. Kellner observed that, in the medically ill, secondary thanatophobia is more common than primary thanatophobia (Kellner, 1986). Moreover, mental pain encompasses aspects related to catastrophizing on the consequence of psychological suffering (e.g., "My pain never go away") and the literature showed a relationship between the misinterpretation of symptoms and thanatophobia (Fabbri et al., 2007).

DCPR-R persistent somatization was found more frequent in migraine subjects with high mental pain, and it could be explained by the fact that migraine subjects with high mental pain are in large majority CM and have more severe depressive symptoms. The literature shows that CM with comorbid depression have the highest rates of functional somatic symptoms (Minen et al., 2016).

No data are available on the relationship between migraine, mental pain, and DCPR-R anniversary reaction. To be noted that the incidence of anniversary reaction was found to be more than ten times higher in migraine subjects with high mental pain than in other clinical population such as patients undergoing heart transplantation and patients with functional gastrointestinal disorders (Fabbri et al., 2007).

The levels of ES well-being and ES psychological flexibility were found statistically significant lower in migraine subjects with high mental pain with respect to those observed in migraine patients with low mental pain. No data are available

concerning this relationship. However, Fava conceptualized the well-being as resulting from the balance between euthymia and mental pain (Fava, 2016a); thus, according to the concept of balance, migraine subjects with high mental pain could also represent the migraine population with poor euthymia.

Migraine subjects with high mental pain showed higher statistically significant CID scores than migraine subjects with low mental pain concerning: feelings of depressed mood; guilt, lowered self-esteem, and worthlessness; pessimism and hopelessness; suicidal tendencies; work and interests; energy and fatigue; anxiety psychic, generalized; total score depressive symptoms; total score anxiety. These findings are consistent with the literature which describes mental pain and severe depressive symptoms as strictly intercorrelated (van Heeringen et al., 2010). Moreover, these findings are consistent with the literature showing that mental pain is a psychological dimension that encompasses guilt, fear, grief, hopelessness, anger, anxiety, and irreversibility (Shneidman, 1998; Bolger, 1999; Orbach et al. 2003).

Compared with migraine subjects with low mental pain, migraine subjects with high mental pain showed statistically significant impairment in all PSI psychosocial dimensions. Again, no data are available in the literature on this issue. However, some studies showed that mental pain is associated with social pain (i.e., psychological suffering due to a psychosocial impairment) (Eisenberger et al., 2003). Mental pain, social pain, and bodily pain were found to share a common neural pathway (i.e., increased activity in the anterior cingulate cortex and the right ventral prefrontal cortex) (Eisenberger et al., 2003). Moreover, social pain is included in the description of acute psychological suffering that mental pain entails (e.g., disruption in the person's tendency toward maintaining a sense of wholeness and social unity, loss of meaning in life, disconnection from a loved one) (Frankl, 1963; Bakan, 1968; Bolger, 1999). Thus, it could be hypothesized that migraine subjects with mental pain have also higher social pain rising from psychosocial impairment.

Univariate logistic regression showed that the statistically significant risk factors for mental pain in migraine subjects were CID depressive symptoms, PSI psychosocial distress, and PSI stress. When a multivariate logistic regression model of risk factors was run, depression and psychosocial distress survived. These findings are consistent with the literature highlighting a relationship between severe depression, severe distress, and mental pain (Shneidman, 1998; Orbach et al. 2003; van Heeringen et al., 2010).

Univariate logistic regressions showed that ES well-being, ES psychological flexibility, PSI well–being, and PSI quality of life were statistically significant protective factors for having mental pain in migraine. When multivariate analyses were run, only ES well-being and PSI well-being survived as protective factor. These results can be explained under the light of evidence showed by Eisenberger

and colleagues (Eisenberger et al., 2003); they showed that the mental pain aroused form the activation of the common neural pathways shared by physical and social pain (Eisenbergeret al., 2003). Thus, it could be hypothesized that ES well-being and PSI well-being work as protective factors in these two domains. In fact, ES well-being encompasses protective factor from headache attacks (i.e., physical pain) (e.g., restorative sleep, feeling of cheerful, calm, and relaxation) (Minen et al., 2016) and psychosocial well-being protects migraine patients from the activation of social pain that could arouse form the impairment of family functioning, working activities, and interpersonal domains (MacDonald & Leary, 2005). Thus, protective factors for social pain and physical pain might protect migraine patients from mental pain.

6.5 Limitations and Strengths

This study has limitations and strengths. The first limitation is the mono-centricity of the research and the use of a third-level facility for the enrolment, thus the results cannot be generalized to migraine subjects of the general population. However, third-level facilities are commonly used in research of this kind since the large majority of migraine patients address these centres (McLean & Mercer, 2017). An additional shortcoming, which might limit the generalization of results, is the relatively small sample size, although adequate to run the analyses presented. The main strengths are that DCPR-R-ISS, MPQ, and ES were applied for the first time to assess migraine outpatients according to psychosomatic and clinimetric principles (Fava, Cosci, & Sonino, 2017).

7 Conclusions

Compared with HS, EM had higher rates of DCPR-R psychosocial syndromes in the domains of illness behaviour and concerning the diagnosis of Illness denial. Higher levels of anxious symptoms and PSI psychological distress were found as statistically significant risk factors of EM as compared to HS while a higher level of PSI quality of life was a statistically significant psychological protective factor.
CM showed higher rates of major depressive disorder as well as of depressive and anxious symptoms than HS. CM showed higher rates of DCPR-R allostatic overload, persistent somatization, and illness denial than HS. CM showed higher levels of mental pain and lower levels of ES psychological well-being and psychological flexibility than HS. Psychological distress and mental pain were statistically significant risk factors for CM as compared to HS, whereas ES psychological well-being was found as a protective factor.
CM showed lower rates of DCPR-R persistent somatization and conversion symptoms than EM. CM showed higher CID scores and higher levels of mental pain than EM. CM showed a lower psychosocial functioning assessed via the PSI, a lower ES psychological well-being, and a lower ES psychological flexibility than EM. PSI psychological distress and mental pain were found risk factors for CM as compared to EM, while PSI well-being and ES well-being were found as protective factor.
Migraine subjects with mental pain showed higher rates of DSM-5 mental disorder, higher rates of depressive symptom assessed via the CID, higher rates of DCPR-R diagnosis of allostatic overload, demoralization, thanatophobia, anniversary reaction, and persistent somatization than migraine subjects without mental pain. ES well-being and ES psychological flexibility were statistically significant lower in migraine subjects with high mental pain than in those with low mental pain. Compared with migraine subjects with low mental pain, migraine subjects with high mental pain showed statistically significant impairment in all the PSI psychosocial dimensions. CID depression and PSI psychosocial distress were found as statistically significant risk factor for mental pain in migraine, whereas ES well-being and PSI well-being were found protective factor.

In conclusion, an assessment of migraine subjects which aims at being comprehensive according to clinimetric and psychosomatic principles (Fava, Cosci, & Sonino, 2017) should include the Diagnostic Criteria for Psychosomatic Research-Revised (DCPR-R), the Mental Pain Questionnaire (MPQ), and the Euthymia Scale (ES). Mental pain is a psychosomatic variable deserving attention in chronic

migraine patients. ES Well-being is a protective factor for both chronic migraine and mental pain.

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