PSYCHOLOGICAL FACTORS AS DETERMINANTS OF MEDICAL CONDITIONS,
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PSYCHOLOGICAL FACTORS AS DETERMINANTS OF MEDICAL CONDITIONS,
2nd Edition

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EDITORIAL
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Editorial: Psychological Factors as Determinants of Medical Conditions

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Editorial on the Research Topic

Psychological Factors as Determinants of Medical Conditions

Life expectancy is increasing world-wide and age-related diseases are becoming a major health concern. It is known that chronic diseases and related outcomes may seriously impact people's perceived quality of life, and this effect may in turn lead to psychopathological consequences. Indeed, psychopathological symptoms frequently occur in chronic medical conditions and can even predict and impact mortality independently of a wide range of potential confounders.

This Research Topic includes interdisciplinary and multidisciplinary contributions in order to understand how psychopathological aspects may seriously impact somatic symptoms and medical outcomes, especially in age related common chronic diseases. The scientific interest in understanding how psychological factors may determine several medical conditions is dramatically growing. In keeping with this awareness, the current Research Topic aimed to provide a significant contribution to this field by inspiring the submission of scientific articles promoting a multi/inter-disciplinary approach, and suggesting a new direction in psychopathological research and prevention, leading to screening subjects at risk for medical events in order to individualize and improve diagnostic and therapeutic approaches. Our collection includes 15 research articles that explore the reciprocal link between psychological determinants and medical conditions with regard to three fundamental domains: cognition, stress, and emotion. Five articles, particularly, explored the influence of ADHD (Klein et al.), metabolic syndromes (Guicciardi et al.; Marchini et al., 2018; Settineri et al., 2019), early life stress (Péterfalvi et al.), viral infections and mental health issues on cognitive processes; five articles explored the influence of stress on metabolic syndromes (Kelly et al.; Martino et al.), quality of life in liver transplant recipients (Funuyet-Salas et al.), autoimmune diseases (Cataudella et al.), mental health of workers, perceived pain during upper endoscopy (Lauriola et al..), and fibromyalgia and rheumatic diseases (Marchi et al.); lastly, three articles provided a contribution to the link between emotion processing and/or mood diseases in psoriasis (Ciuluvica et al.), psychosomatic disorder (Settineri et al.), and pain therapy (Fiegl et al.).

Much more effort needs to be done and many issues remain to be addressed to boost our knowledge with special regard to psychological factors as determinants in the setting of medical disease (Mangelli et al., 2005). Overturning the usual causal direction body-mind, evidence exists regarding the key role of psychopathological factors in the history of chronic illness. It is known in fact that a strict evaluation of the psychological variables could contribute to a better understanding of the individual condition and possibly predict the risk of onset of new medical diseases or complications. Several studies have emphasized, in chronic diseases, the neuropsychological functioning in chronic diseases (Catalano et al., 2019), even in ADHD (Martino et al., 2017; Fabio et al., 2018; Salehinejad et al., 2019)

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and it is known that the neuropsychological evaluation may reflect also the involvement of the frontal lobe functions (Bechara and Noel, 2010; Vicario and Martino, 2010). It could be furthermore interesting to provide more work on the mechanisms underlying the relationship between clinical psychological symptoms as anxiety, depression and health related quality of life, and chronic medical conditions among which we can consider metabolic, bone, celiac, and thyroid diseases (Misra and Lager, 2008; Di Corrado et al., 2013; Smith et al., 2013; Castelnuovo et al., 2015; Del Piccolo et al., 2015; Catalano et al., 2017, 2018; Guicciardi, 2017; Le Donne et al., 2017; Martino et al., 2018a,b, 2019). It would be also interesting to investigate how negative emotions, such as anger and disgust, are linked to different psychopathological conditions, such as depression and personality disorders (Vicario, 2013; Craparo et al., 2016; Vicario et al., 2017). It would be also exciting to explore how the treatment of psychological factors determinants of several medical conditions can be enriched by different therapeutic approaches, including the use of non-invasive brain stimulation technologies, which are known to be effective for the treatment of psychopathological conditions (Vicario and Nitsche, 2013a,b; Gangemi et al., 2018; Vicario et al., 2019).

These examples from the studies of this Research Topic are representatives of many endeavors that may deepen our understanding of the link between psychological factors and medical conditions. In conclusion, we seek to advance the knowledge with special regard to the psychological factors as determinants of medical conditions by highlighting specific psychological characteristics which may facilitate prevention, intervention approach and plans. Moreover, we trust that deepening our understanding of these topic may help researcher and clinicians to develop prevention strategies which will improve mental health and quality of life.

It has been a great pleasure and honor to be involved in this Research Topic. We would like to thank all the Authors, Reviewers, and the entire Frontiers Editorial and Developmental Staff for helping and assisting to make this Research Topic possible. Our satisfaction leads us to look forward with pleasure and interest to further address the links between psychological factors and medical conditions in future work.

AUTHOR CONTRIBUTIONS

GM and CV wrote the first draft of the manuscript and revised it critically. VL and VC provided opinions on it. GM, CV, VL, and VC read and approved the submitted version.

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REVIEW
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Impacts of Psychological Stress on Osteoporosis: Clinical Implications and Treatment Interactions

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The significant biochemical and physiological effects of psychological stress are beginning to be recognized as exacerbating common diseases, including osteoporosis. This review discusses the current evidence for psychological stress-associated mental health disorders as risk factors for osteoporosis, the mechanisms that may link these conditions, and potential implications for treatment. Traditional, alternative, and adjunctive therapies are discussed. This review is not intended to provide therapeutic recommendations, but, rather, the goal of this review is to delineate potential interactions of psychological stress and osteoporosis and to highlight potential multi-system implications of pharmacological interventions. Review of the current literature identifies several potentially overlapping mechanistic pathways that may be of interest (e.g., glucocorticoid signaling, insulin-like growth factor signaling, serotonin signaling) for further basic and clinical research. Current literature also supports the potential for cross-effects of therapeutics for osteoporosis and mental health disorders. While studies examining a direct link between osteoporosis and chronic psychological stress are limited, the studies reviewed herein suggest that a multi-factorial, personalized approach should be considered for improved patient outcomes in populations experiencing psychological stress, particularly those at high-risk for development of osteoporosis.

Keywords: osteoporosis, bone, psychological stress, mental health, depression, PTSD, pharmacology, alternatives

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BACKGROUND

Emerging evidence points to the potential pathological impact of mental health on disease. It has long been held that stress has negative impacts on health and disease risk, but the specific mechanisms by which this occurs, as well as implications for treatments and clinical recommendations, have not been examined in-depth. This review will provide an overview of recent literature regarding the impact of psychological stress and stress-related disorders, such as post-traumatic stress disorder (PTSD), depression, and anxiety, on risk and treatment of osteoporosis. In this review, we first highlight mechanisms that impact both bone health and mental health toward identification of potentially overlapping signaling pathways. We then review current literature regarding the impact of common therapeutic agents for treatment of osteoporosis and mental health disorders. This will promote recognition of the potential interaction of these therapeutic agents in patients with concurrent mental health disorders and osteoporosis to encourage a broad view of disease management toward improved patient health.

Finally, we provide a perspective outlook on the potentially beneficial effects of alternative treatments, such as exercise and nutritional supplementation, on both osteoporosis and psychological stress.

OSTEOPOROSIS

There are four major bone cell types: osteoclasts, osteoblasts, osteocytes, and osteogenic stem cells. Osteoclasts, which are of myeloid origin, are giant, multinucleated cells that adhere to the bone and resorb it through acidification and proteolytic digestion. Osteoblasts counteract osteoclast-mediated bone resorption by secreting osteoid, which mineralizes to form new bone. There is a tightly-regulated balance between osteoclast-mediated removal of old or damaged bone and osteoblast-mediated replacement of new bone to maintain bone mass and skeletal homeostasis. After secretion of osteoid, osteoblasts either become trapped within the osteoid and terminally differentiate into osteocytes, quiesce into bone lining cells, or undergo apoptosis. Osteocytes comprise 90–95% of the bone cell population (1). Once they become embedded in the mineralized tissue, they develop cytoplasmic projections that intercalate throughout the bone, creating a signaling network to communicate directly with other osteocytes (2). Through this network, osteocytes regulate phosphate homeostasis and transduce mechanical stress signals into biologic activity to stimulate either bone resorption or formation. Osteogenic stem cells are the source of osteoblasts and osteocytes and are involved in bone repair, regeneration, and development. The functions and number of these cell types can become disrupted following bone damage or in disease states, such as osteoporosis.

Osteoporosis is the most common form of metabolic bone disease and is characterized by low bone mass and micro-architectural bone deterioration. The World Health Organization defines osteoporosis as a bone mineral density (BMD) that is $\leq$2.5 standard deviations below peak bone mass, which is typically achieved around age 30. In the United States alone, osteoporosis accounts for over 1.5 million fractures per year (3). By 2025, treatment costs are estimated to exceed $25 billion (4). Osteoporosis is characterized by an imbalance of skeletal remodeling, resulting in increased osteoclast activity and/or decreased numbers of osteoblasts, which can lead to decreased bone strength and mass, as well as increased susceptibility to fracture.

Osteoporosis is an umbrella term for a group of distinct pathological conditions and has been traditionally classified into primary and secondary types based on mechanism of disease (5). There are two main types of primary osteoporosis: type I osteoporosis and type II osteoporosis. Type I osteoporosis occurs most frequently in postmenopausal women and primarily results from estrogen deficiency. Estrogens inhibit production of receptor activator of nuclear factor kappa-B ligand (RANKL), which is crucial for osteoclast differentiation and recruitment, as well as interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF-α) (6, 7). In addition, estrogens promote osteoblast differentiation and positively regulate several anabolic bone-related proteins, including insulin-like growth factor-1 (IGF-1), bone morphogenetic proteins (BMPs), and procollagen type I (COL1) (8). Thus, postmenopausal decrease in estrogen may affect both bone resorption and bone formation. The functional outcome is a rate of bone resorption that is higher than that of bone formation, resulting in a net decrease in bone mass. Type II osteoporosis is associated with aging and is commonly observed in men and women after the age of 60. Aging results in a progressive decline in osteoblast numbers and decreased osteoblast activity, but no change in osteoclast activity. It is still unknown how the cellular and molecular mechanisms that contribute to these two primary types of osteoporosis compare to each other or to what extent sex steroid deficiency contributes to age-related skeletal degradation. Findings in mouse models suggest that the effects of age on skeletal health are independent of estrogens, but data describing a similar mechanism in humans is lacking (9, 10).

Secondary osteoporosis is characterized by bone loss resulting from an underlying etiology, such as Cushing's syndrome, or prolonged treatment with glucocorticoids. In glucocorticoid-induced osteoporosis, bone loss occurs within several months of glucocorticoid treatment and can lead to significant decreases in cancellous bone mass and increased fracture risk. Excess glucocorticoids exert an inhibitory effect on osteoblast differentiation (11). Glucocorticoid-induced osteoporosis is the most common form of secondary osteoporosis and is the most common form of osteoporosis among young people [reviewed in Briot and Roux (12)]. Secondary osteoporosis can also be caused by disuse. Prolonged bone unloading, as seen in extended bed rest or space travel, inhibits bone formation and enhances bone resorption. This occurs due to the lack of appropriate regulation of bone mass by the osteocyte network and, possibly, through involvement of the sympathetic nervous system (13).

Although decreased BMD is what defines osteoporosis, this factor alone is not a major cause of pain or morbidity. Instead, morbidity associated with osteoporosis is primarily due to increased incidence of fragility fracture. Due to the biomechanical and biological alterations in osteoporotic bones, only a minor external force, such as a short fall, is required to induce a fracture. Osteoporotic fractures are three times more likely in women and typically occur after the age of 50 (14). Not only does osteoporosis increase fracture

Abbreviations: ALP, Alkaline Phosphatase; ASD, Acute Stress Disorder; BDNF, Brain-Derived Neurotrophic Factor; BMD, Bone Mineral Density; BMPs, Bone Morphogenic Proteins; CNS, Central Nervous System; COLI, Procollagen Type I; DHA, Docosahexaenoic Acid; EPA, Eicosapantaenoic Acid; FDA, Food and Drug Administration; GABA, Gamma-Aminobutyric Acid; GAD, Generalized Anxiety Disorder; H_2O_2, Hydrogen Peroxide; HPA, Hypothalamic-Pituitary Adrenal; IGF-1, Insulin Growth Factor-1; IGFBPs, Insulin Growth Factor Binding Proteins; mTOR, Mammalian Target of Rapamycin; MDD, Major Depressive Disorder; MSCs, Mesenchymal Stromal Cells; NFκB, Nuclear Factor Kappa B; NMDAR, N-methy-D-aspartate receptor; OCN, Osteocalcin; OPG, Osteoprotegerin; PTH, Parathyroid Hormone; PTHR1, Parathyroid Hormone Receptor-1; PTSD, Post-Traumatic Stress Disorder; QOL, Quality of Life; RANKL, Nuclear Factor Kappa B Receptor Ligand; ROS, Reactive Oxygen Species; SAM, Sympathomedullary; SERMs, Selective Estrogen Receptor Modulators; SSRI, Selective-Serotonin Reuptake Inhibitors; TGFβ, Transforming Growth Factor-β; TNF-α, Tumor Necrosis Factor-α.

risk, but it is also associated with poorer fracture healing outcomes [reviewed in Cheung et al. (15)]. Current treatment strategies are aimed at increasing calcium and vitamin D levels through supplementation, inhibiting bone resorption through bisphosphonate administration, and mitigating the effects of menopause through hormone replacement (discussed in detail below). The FDA has also approved the anabolic agent, human parathyroid hormone (PTH) peptide, to treat osteoporosis. In addition, newer therapies, such as strontium ranelate administration and antibodies against RANKL, are being investigated (16). Stem cell therapies are being examined for their ability to enhance repair of fractures (17). Transplantation of allogeneic non-osteoporotic stem cells may be able to normalize the aberrant bone remodeling that occurs in osteoporotic patients, thereby reducing fracture risk (18). However, the optimal stem cell phenotype and method of delivery are still poorly characterized (19). There is an ongoing need to identify, develop, and improve therapeutics that reduce fracture risk, enhance bone mineral density, and promote fracture healing.

PSYCHOLOGICAL STRESS

Psychological stress is defined as an emotional experience that is accompanied by predictable biochemical, physiological, and behavioral changes (20). Psychological stress can occur in response to an acute event, as in a fight-or-flight response to a life-threatening or traumatic event, or stress can be chronic, as in the case of caregivers, service members, and high-stress occupations. In acute psychological and physical stress, stress signaling is initiated through the hypothalamic-pituitary-adrenal (HPA) axis and the sympathomedullary (SAM) pathway via secretion of stress hormones, which include glucocorticoids (cortisol) and catecholamines (epinephrine, norepinephrine). Immune cells (leukocytes) express receptors for these hormones (glucocorticoid receptors and adrenergic receptors, respectively) and rapidly respond to their induction by altering the inflammatory immune response. However, in chronic stress and chronic stress-associated mental health conditions, the HPA-axis becomes dysregulated, resulting in hypercortisolism or glucocorticoid resistance (21). Whether the stress response becomes pathologic is dependent on many factors, including individual coping skills, life history, severity, and duration of the stressor.

Anxiety or depression disorders can arise as a result of acute or chronic stress. Depressive mood disorders, such as major depressive disorder (MDD), are characterized by persistent emotional and physical symptoms, including depressed mood, loss of interest and enjoyment (anhedonia), and dysregulated sleep. Depression is often comorbid with anxiety, and both conditions can alter the HPA response. Anxiety can manifest as excessive worry, fear, irritability, difficulty concentrating, and with physical symptoms, such as increased heart rate and breathlessness. Mental health disorders, such as depression, result in a variety of potentially detrimental biochemical and physiological changes [reviewed in Yang et al. (22)]. Other stress-related conditions include acute stress disorder (ASD), in which individuals experience a constellation of symptoms, such as anxiety, flashbacks, and distress related to and surrounding a traumatic event. When these symptoms persist beyond the acute phase of 1 month, they are recognized as the chronic condition, termed post-traumatic stress disorder (PTSD). PTSD is recognized as an extreme case of chronic stress in which symptoms can persist for months to years. It is defined by display of symptoms that include heightened response to events or circumstances related to an initial traumatic and/or life-threatening event. Symptoms of PTSD are both intrusive, such as flashbacks and unwanted upsetting memories, and avoidant, such as evasion of stimuli that could recall the initiating trauma. Together, these symptoms have a significant impact on patient quality of life (QOL) and can lead to severe anxious, depressive, and debilitating effects (23). PTSD impacts approximately 3.6% of individuals annually, with increased incidence among Veteran populations, for whom rates have approached 20% in those returning from recent conflicts in Afghanistan and Iraq (24, 25). Estimates of the number of individuals with mental health disorders, or even those experiencing short-term psychological stress, are difficult to obtain, partially owing to the fear of stigmatism and rejection that may accompany mental health disorder diagnosis. Nonetheless, mental health disorders impact a significant percentage of the population, and it is becoming increasingly clear that psychological stress has significant impact on patient QOL, as well as physical health.

PSYCHOLOGICAL STRESS AS A RISK FACTOR FOR OSTEOPOROSIS

Psychological stress can have lasting impact on risk for development of comorbid disease, as well as significant impact on pre-existing diseases. Chronic stress has been associated with obesity, atherosclerosis, lung pathologies, and diabetes (26, 27). In regard to osteoporosis, U.S. military veterans diagnosed with PTSD have a higher risk of developing osteoporosis (28), as do civilians with PTSD diagnosis (29). Likewise, it was found that among 73 female Holocaust survivors there was a 3.47-fold increase in prevalence of osteoporosis compared to controls (30), suggesting psychological stress may be a risk factor for osteoporotic disease. However, malnutrition and other factors likely played a role as well, although the authors did not discuss this possibility. A recent mouse study by Foertsch et al. showed that chronic stress induced by a chronic subordinate colony housing model of PTSD resulted in reduced growth plate endochondral ossification in adolescent mice (31). Increased expression of tyrosine hydroxylase (a catalytic enzyme involved in catecholamine biosynthesis) by bone marrow cells located in the growth plates of the femurs of chronically stressed mice suggested that decreased bone length and density may be due to stress-induced catecholamine impact on bone growth.

While the mechanisms underlying the physiological and biochemical impact of psychological stress on disease are not well-understood, several studies have shown that stress hormone signaling via the brain-immune connection is a significant contributor (32). Chronic stress has been associated

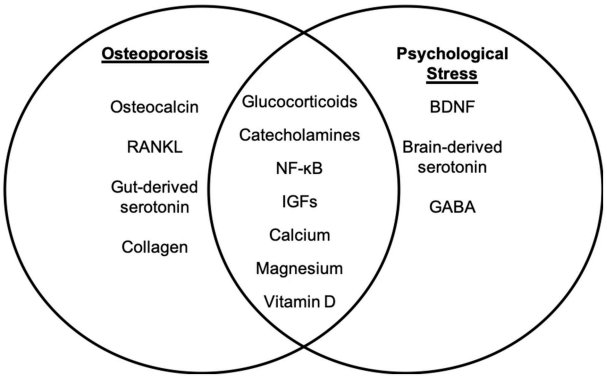

FIGURE 1 | Molecular targets of osteoporosis and psychological stress. While psychological stress and osteoporosis occur via distinct mechanisms, there are several factors that overlap between psychological stress-associated mental health disorders and osteoporosis. The molecular factors that are distinct to osteoporosis **(left panel)** and psychological stress **(right panel)** are listed. Intersecting factors related to osteoporosis and psychological stress are listed in the **(middle panel)**.

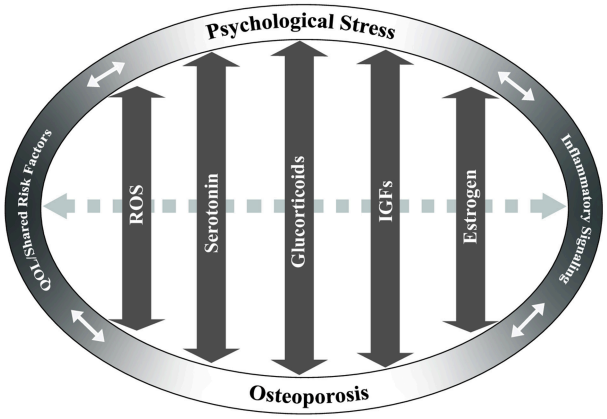

FIGURE 2 | Potentially overlapping pathways of osteoporosis and psychological stress. Key pathways that may have overlapping effects between chronic stress and osteoporosis are identified based on current literature. These include reactive oxygen species (ROS), serotonin, glucocorticoid, insulin-like growth factor (IGF), and estrogen signaling pathways. Arrows indicate the potential of these pathways/factors to influence both chronic stress and osteoporosis in a bi-directional fashion. Dashed gray arrow between pathways indicates potential interactions between the pathways. Quality of life (QOL)/shared risk factors and inflammatory signaling are positioned at ends of ellipse to demonstrate cross-effects between chronic psychological stress and/or osteoporosis.

with increased systemic inflammation (26, 27, 33) and altered hematopoiesis (34). Inflammatory factors have been shown to have a detrimental effect on osteoporosis through promotion of osteoclast differentiation and apoptosis of osteoblast populations [reviewed in Eastell et al. (35)]. It has also been suggested that a number of inflammatory factors may actually exhibit inhibitory effects on osteoclast activity, thereby potentially improving bone health in osteoporosis (36). Thus, while common to both conditions, the roles of inflammatory factors in osteoporosis and in psychological stress are likely highly complex and both context- and dose-dependent. A review of the current literature identifies several additional pathways and cellular mechanisms that are common to chronic psychological stress and osteoporosis. Literature is limited in terms of studies examining any direct mechanistic interaction between these pathways in the context of osteoporosis and psychological stress; however, independent examination of the mechanisms of disease and shared risk factors suggests that further research is warranted. The studies below, and summarized in **Figures 1** and **2**, discuss several of these common pathways, cellular and molecular mechanisms, and risk factors to highlight the potential for future examination of the role of chronic psychological stress/mental health on osteoporosis.

Glucocorticoids

In chronic psychological stress, dysregulated glucocorticoid signaling has profound impacts on inflammation and may also contribute to disease risk (21). Stress-induced dysregulation of endogenous glucocorticoids may mimic the skeletal effects of glucocorticoid-induced osteoporosis. Glucocorticoids are hormones that exert their effects largely by entering the nucleus and modulating gene transcription. Glucocorticoid-responsive transcription factors are primary regulators of inflammation resulting from stress hormone signaling and include NF-κB. There is some evidence to suggest that activation of NF-κB through glucocorticoid responsive elements in response to psychological stress may contribute to the risk of osteoporosis through RANK signaling (37). In addition, glucocorticoids are known to act directly on bone cells, leading to decreased osteocyte viability, decreased osteoblast function due to reductions in IGF-2, and prolonged osteoclast viability [reviewed in Briot and Roux (12)]. Therefore, psychological stress may negatively impact bone health through modulation of endogenous glucocorticoids.

Catecholamines

Catecholamines are stress hormones that include norepinephrine, epinephrine, and dopamine. Norepinephrine and epinephrine are released by the adrenal glands as part of the rapid fight-or-flight response to stress. This elevation is typically in response to a physical stressor; however, psychological stress (e.g., sudden bad news, fear, or PTSD-related flashbacks) can also trigger catecholamine release. Chronic and/or repeated elevations in norepinephrine or epinephrine in response to psychological stress may contribute to the development of depression (38). Dopamine is also increased in specific brain regions in response to pain or stress. Like other catecholamines, dopamine may become dysregulated in the case of chronic stress [reviewed in Vaessen et al. (39)].

One way in which psychological stress may impact osteoporotic disease risk and severity is through catecholamine-induced activation of β-adrenergic receptors on osteoblasts and osteoclasts. β-adrenergic receptor activation has been shown to increase RANKL expression, resulting in osteoclast differentiation (40). Treatment with a β-agonist resulted in

bone loss due to increased bone resorption (41). β-adrenergic signaling was also shown to exacerbate bone loss through promotion of osteoclastogenesis via generation of reactive oxygen species (ROS) (42). These studies suggest that alterations in catecholamines due to chronic stress may impact bone health and contribute to risk and severity of osteoporosis.

Myeloid Populations

Chronic psychological stress has been shown to alter myeloid phenotype and increase myelopoeisis. Activation and increased contribution of myeloid populations are significant in that myeloid-derived immune cells are the primary mediators of the inflammatory response promoted by chronic stress (43). The myeloid response to chronic stress may significantly contribute to bone health and osteoporotic disease, given that osteoclasts are myeloid-derived, and monocytes are well-known for their plasticity during wound repair. However, the role of myeloid cells in bone health is complex. Depletion of macrophages in mice was shown to lead to early skeletal growth retardation and osteoporosis and decreased the number of bone marrow-derived mesenchymal stromal cells (MSCs) present in the bones (44). Further, these so-called "osteomacs" were shown to be closely associated with areas of bone remodeling and were directly involved in formation of the canopy structure that makes up the bone-remodeling compartment. Depletion of osteomacs caused complete loss of this compartment. However, removal of osteomacs from calvarial cultures decreased markers of osteoblastic function, including osteocalcin (OCN) mRNA expression and mineralization *in vitro*. Thus, targeting the myeloid cell population as an osteoporotic treatment may not be an optimal approach due to the duality of its effects.

Insulin-Like Growth Factors (IGFs)

Glucocorticoids and IGFs are known to regulate one another, suggesting that mood may influence levels of IGF-1 (45, 46). IGFs may also play a role in psychological stress (47) and osteoporosis (48). Circulating IGF-1 is increased in individuals with depression or anxiety disorders (49, 50) and has been shown to be a biomarker for vulnerability of an individual to stress following traumatic brain injury (51). Yu et al. found that, in a single prolonged stress model, IGF-1 levels were up-regulated by approximately 25% in the stressed group, although this data was not statistically significant (52). Another study by Hoshaw et al. demonstrated an anti-depressant and anti-anxiolytic effect of IGF due to its effects on serotonin (53). These conflicting reports suggests that further research is needed to determine whether IGF has beneficial or detrimental impacts on psychological stress-related mental health disorders.

In bone health, IGF-1 and−2 regulate osteoblast-osteoclast interactions, thus making them important regulators of bone remodeling (54). IGF-1 has also been shown to activate mammalian target of rapamycin (mTOR) remodeling to stimulate MSC differentiation into osteoblasts (55). Knockout of IGF-1 impairs osteoblast differentiation and leads to decreased trabecular bone formation (56). Its role in fracture healing is still not fully understood, as some studies suggest beneficial effects of IGF-1 treatment, while other studies demonstrate non-significant effects (57–59). IGF-1 action and circulating levels also decline with age, and this mechanism has been suggested to be an underlying cause of age-related osteoporosis [reviewed in Perrini et al. (60)]. IGF-2 is most commonly thought of as a fetal growth factor; however, it is the most abundant growth factor stored in adult bone. Induction of the osteogenic lineage from parthenogenetic embryonic stem cells is enhanced with IGF-2 treatment (61). Interestingly, different effects of IGF-1 vs. IGF-2 have been reported in human bone cell metabolic pathways, suggesting they activate different signaling cascades, even though they both primarily signal through the IGF1R (62, 63). The differing effects of IGF-1 and IGF-2 could be due to cell-specific expression patterns. It is also possible that the presence and concentration of specific insulin-like growth factor binding proteins (IGFBPs), which mediate IGF bioavailability and are temporally and spatially regulated, may regulate these differing effects. Together, these studies suggest IGF as a potential connecting pathway between osteoporosis and psychological stress. Additional studies are needed to delineate the role of IGF-1 vs. IGF-2 and to determine how IGFBPs (64) may be temporally and differentially regulated during osteoporosis, psychological stress, and in osteoporotic patients who have a history of mental health disorders.

Oxidative Stress

Studies on depressive disorders have shown a significant decrease in neuronal and glial cells in depressed patients. It has been suggested that the decline in these populations is due to an increased amount of ROS [reviewed in Michel et al. (65)]. ROS have been shown to induce osteoblast apoptosis, leading to decreased bone formation (66, 67). ROS, as well as hydrogen peroxide (H_2O_2), are required for RANKL-induced osteoclast generation (68–70). Further, increased ROS in the bone marrow compartment can lead to expansion of lymphocytes, altered cytokine production (71, 72), and promotion of osteoclastogenesis (42). In regard to impacts on osteoporosis, ovariectomized rats were found to have increased oxidative stress compared to controls. However, treatment with palm tocotrienol, a potent antioxidant, for 8 weeks resulted in suppression of malondialdehyde levels, a marker of oxidative stress, and promotion of plasma glutathione peroxidase and erythrocyte superoxide dismutase activity, two key antioxidant enzymes (73). Thus, palm tocotrienols may have bone protective effects by limiting oxidative stress damage [reviewed in Chin and Ima-Nirwana (74)].

Serotonin

Serotonin, or 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter that is involved in a host of important processes, including sleeping, eating, digesting, and mood regulation [reviewed in Sangkuhl et al. (75)]. Serotonin is synthesized both in the gut and in the brain by different isoforms of tryptophan hydroxylase (TPH), TPH-1 and TPH-2, respectively. The vast majority (95%) of serotonin is produced in the periphery, mainly by enterochromaffin cells in the duodenum. Until recently, it has been thought that serotonin

does not interact with bone; however, recent studies have begun to unmask a complex role for serotonin in regulating bone mass and bone metabolism [reviewed in Wadhwa et al. (76)]. Serotonin has been shown to regulate osteoblast proliferation and function *in vitro* (77), and osteoblasts and osteoclasts express a variety of serotonin receptors (Htr1a, Htr1b, Htr1d, Htr2a, Htr2b) (78, 79). Addition of serotonin to RAW264.7 cells induced osteoclast differentiation through intracellular accumulation of serotonin via the serotonin transporter (SERT or 5-HTT), resulting in upregulation of NF-κB (80). When produced peripherally, serotonin inhibits bone formation and decreases osteoblast proliferation [reviewed in Ducy and Karsenty (81)]. When produced in the brain, serotonin acts as a neurotransmitter to exert a positive effect on bone mass accrual by enhancing bone formation and limiting bone resorption via regulation of the sympathetic response [reviewed in Dimitri and Rosen (82)].

Shared Risk Factors

Several independent lifestyle risk factors for development of osteoporosis may also be impacted by concurrent stress-associated mental health disorders, such as smoking, alcohol use, and substance abuse. Smoking, in particular, represents a strong risk factor for development of osteoporosis. The direct mechanism(s) by which this occurs are not well understood. However, a study by Ko et al. demonstrated that serum from animals exposed to smoking resulted in increased osteoclast differentiation from macrophages in response to RANKL, as well as a reduction in alkaline phosphatase (ALP) and consequent reduction in osteoblast differentiation (83). In patients seeking mental health care, 28.2% report smoking, as compared to 17.5% among the general population (84). This finding suggests that psychological stress is associated with an increased risk for smoking. Due to the reported negative impact of smoking on bone health (85), psychological stress may also indirectly increase risk of osteoporosis. Similarly, alcohol consumption is a significant risk factor for development of osteoporosis (86, 87), due, in part, to senescence and ROS production in bone marrow-derived MSCs, which results in decreased osteogenic potential (88). Substance abuse, such as opioid addiction, is also elevated among those suffering with psychological stress-associated mental health disorders (18.7 vs. 5% among those without mental health disorders) (89). Increased rates of osteopenia and osteoporosis have been found among women addicted to opioids (90).

Obesity may represent another risk factor for osteoporosis, due to increased inactivity, leading to cases of unloading. Likewise, as described below, exercise may provide benefit for BMD and in reducing fracture risk. In addition, obesity leads to increased systemic inflammation, with many of the signals, such as NF-κB and TNF-α, being differentiation factors for osteoclasts as well. There is also a clear link between obesity and development of type 2 diabetes, which is another known risk fracture for development of osteoporotic fracture [reviewed in Walsh and Vilaca (91)]. However, weight gain, itself, may have positive effects on osteoporosis. Weight loss in postmenopausal women was shown to increase risk of frailty fractures (92). Conversely, weight gain reduced risk of hip fractures, although it does increase risk of other types of fracture (93, 94). Clearly, the effects of weight on fracture are complex and require further study.

Together, these studies indicate that, in patients with extreme and/or chronic psychological stress, osteoporotic risk may be exacerbated by compounded effects of these common risk factors. As such, in addition to independent risk factors for osteoporosis, the potential for a multifactorial feedback loop with psychological stress exists and should not be overlooked.

INTERACTION OF TREATMENTS

Based on the studies above demonstrating potentially overlapping factors, cellular mechanisms, and signaling pathways between osteoporosis and chronic psychological stress, it is not surprising that treatments for these conditions may also have overlapping and opposing effects. Thus, it is critical that the interplay between stress and disease-mediated pathways is considered during the planning of best course of treatment for an osteoporotic patient, particularly one with a history of mental health disorder. While this review does not provide, and is not intended to provide, clinical recommendations, a discussion of current literature and potential crosstalk between treatments for osteoporosis and psychological stress-related mental health disorders is provided to encourage consideration of the implications of drug selection from a broad, whole-health perspective.

Osteoporosis Treatments

Given the potential impact of psychological stress and its treatments on bone health, treatments that benefit both bone and mental health may be preferred, especially in patients at high-risk for concurrent osteoporosis and mental health disorders. In this section, we discuss common treatment options for osteoporosis, independent of type, and detail literature that provides evidence of potential impacts of these treatments on mental health. Literature findings outlined below are summarized in **Table 1**. For each osteoporotic treatment, we first discuss its primary use and impacts on bone health, followed by a review of current literature as to its effects on mental health.

It is worth noting that osteoporosis, particularly osteoporotic fracture, may affect mental health and QOL. Osteoporotic fractures can lead to poorer QOL outcomes and negatively impact physical, social, financial, and psychological well-being (95–97). In regard to psychological well-being, osteoporosis can lead to feelings of anxiety, due to fear of falling or fear of fracture, and depression. It has been shown that anxiety and depression are comorbidities of osteoporosis (98), and osteoporotic fracture can cause reduced self-esteem and self-image, likely due to feelings of helplessness and loss of independence (99). All of these factors (loneliness, anxiety, depression, loss of independence, reduced self-esteem, loss of social role, etc.) may, in turn, contribute to disease exacerbation. Effective management of osteoporosis that reduces incidence of osteoporotic fracture (e.g., effective caregiver support) likely provides substantial indirect mental health benefit by preventing these negative outcomes. As

TABLE 1 | Interactions of treatments for osteoporosis and psychological stress.

Drug/therapy	Relevant target	Osteoporosis	Psychological stress	Other considerations
Bisphosphonates	Osteoclasts/bone mineral density	+	?	Potential improvement in mobility, which may improve QOL
Statins	TGFβ pathway	+	+/?	Cardiovascular impacts
Denosumab	RANKL	+	?	
Teriparatide	Parathyroid hormone	+	–/?	
Estrogen/SERM	Multiple	+	+/–	Long-term use could increase cancer risk
Strontium ranelate	Bone mineral density	+	?	
SSRI	Serotonin	-	+	
Benzodiazepines	GABA receptor	-	+	Cardiovascular impacts
Beta-blockers	β-adrenergic antagonist	+	+	Cardiovascular impacts
Barbiturates	GABA receptor	-	+	Addictive; No reversal agent
Fish oil (EPA and DHA)	Unknown/multiple	+	+/?	Cardiovascular impacts
Calcium	Bone mineral density	+	?	Kidney stone development
Magnesium	Bone mineral density	+	+/?	
Vitamin D	Required for calcium absorption	+	+/–	Kidney stone development
Exercise	Multiple	+	+	Multiple health benefits

Treatments for osteoporosis and those for psychological stress potentially interact with each other. Positive benefit is denoted by "+". Negative effects are denoted by "-". Unknown or understudied effects are denoted by "?". Relevant targets in context of osteoporosis or stress are listed. Considerations that may have important clinical impacts are included.

described below, many treatments for osteoporosis may also have direct, biochemical effects on mental health.

Bisphosphonates

Bisphosphonates are antiresorptive agents that bind to hydroxyapatite crystals and become ingested by osteoclasts, where they suppress an enzyme involved in osteoclast-mediated bone resorption. This slows the rate of bone remodeling. In addition, they have been well-documented to reduce fracture risk [reviewed in Crandall et al. (100)]. However, bisphosphonates have negative effects on fracture repair, as they interfere with maturation of cartilaginous callus to mature bone (101). Furthermore, atypical femoral fractures and osteonecrosis of the jaw are two serious side effects of extended bisphosphonate use [reviewed in Black and Rosen (102)]. While bisphosphonates are effective at stalling bone loss, they cannot restore bone mass, as they are antiresorptive and not anabolic. Thus, they may be less effective for patients presenting with severe bone loss.

Bisphosphonates are often the first-choice treatment for osteoporosis, however, there are a limited number of studies, to date, that have examined potential implications of bisphosphonate treatment on mental health. Citraro et al. demonstrated that treatment of ovariectomized rats, a model of osteoporosis, with sodium alendronate had short-term benefit on anxiety and had beneficial impacts on motor performance (103). Reduced immobility, increased distance traveled, and increased mean velocity in behavioral assessments were shown in ovariectomized rats following 3 months of sodium alendronate treatment. However, benefit was not maintained following 6 months of treatment, and short-term benefit can likely be attributed to improved mobility. This suggests that bisphosphonate treatment may provide positive impact on QOL outcomes, due to improved mobility, and may have short-term benefit for anxiety and depression, particularly for patients with type I osteoporosis. An important consideration with bisphosphonate treatment, however, is non-compliance due to incidence of flu-like illness and gastrointestinal upset associated with their use, as well as complicated dosing schedules (104). Non-compliance may be further increased among patients with PTSD, therefore, additional follow-up may be necessary (105). Studies by Kastelan et al. have demonstrated that a monthly, rather than weekly, dosing schedule may also be beneficial toward improving compliance and QOL (106).

Denosumab

Denosumab is a monoclonal antibody to RANKL, a ligand expressed by osteoblasts that is necessary for the differentiation of osteoclasts. Denosumab sequesters RANKL and prevents its interaction with osteoclastic RANK, mimicking the natural function of osteoprotegerin (OPG). The resulting decrease in osteoclastogenesis is associated with significant increases in BMD, which have been shown to continue for up to 10 years of treatment (107). Treatment with denosumab also decreases risk of hip, vertebral, and non-vertebral fractures (108). However, cessation of denosumab leads to a rapid rebound in bone turnover, which has raised concerns over multiple vertebral fractures (109, 110). Denosumab is administered as a subcutaneous injection every 6 months, which has been associated with higher compliance and greater patient satisfaction (111).

The effect of denosumab treatment on mental health is currently unknown. However, Suzuki et al. demonstrated that denosumab treatment altered levels of serum bone-related minerals in osteoporotic patients with rheumatoid arthritis, including alteration of magnesium levels, which is known to impact mental health (described below) (112). Further, recent reports are expanding our understanding of the role of the RANKL-RANK axis outside of the skeletal system [reviewed in

Nagy and Penninger (113)]. RANKL is also expressed by T cells, which is thought to underlie the decrease in BMD associated with diseases of chronic T cell activation (114). RANKL-expressing T cells are known to home to the CNS, where they interact with RANK-expressing astrocytes and microglia (115, 116), cell types with an increasingly apparent role in the central response to chronic stress [reviewed in Calcia et al. (117)]. How denosumab affects immunomodulation of the CNS by RANKL-expressing T cells remains to be elucidated. There is also some evidence to suggest that activation of the sympathetic nervous system, commonly associated with chronic psychological stress, affects the peripheral expression of RANKL on osteoblasts (118, 119) and T cells (120). However, it is currently unknown how altered RANKL expression modulates the efficacy of denosumab in individuals with chronic psychological stress.

Estrogen Replacement Therapy/Selective Estrogen Receptor Modulators (SERMs)

Estrogen replacement can prevent postmenopausal bone loss and reduce fracture risk (121–125). The lack of estrogen in postmenopausal women causes dysregulation of bone cell differentiation, alters osteoblast/osteoclast activity, and induces osteoblast and osteocyte apoptosis, thereby leading to increased bone turnover, with a net effect of resorption exceeding formation (126–128). This is due to increased secretion of pro-inflammatory factors, such as IL-1 IL-6, and TNF-α, as well as estrogen's regulatory role in osteoclast receptor signaling, including RANKL and OPG (129–133). In addition, estrogen loss leads to decreased production of IGF-1, transforming growth factor β (TGFβ), and COL1, all of which are involved in stimulating osteoblast differentiation and activity. Estrogen replacement therapy, in effect, reverses these changes (134–137). However, the anabolic effects of estrogen on bone are dependent on preparation, dose, and route of administration (138). Likewise, estrogen plays a significant role in many tissues throughout the body, so systemic replacement of estrogen creates a complex clinical scenario. For example, a study by the Women's Health Initiative found that estrogen replacement had beneficial effects on fracture and colon cancer risk, but also increased incidence of cardiovascular events, strokes, pulmonary embolisms, and invasive breast cancers (139). Thus, although clearly effective, these systemic effects have lessened enthusiasm for estrogen replacement therapy as the first-line treatment option for osteoporosis (140).

Similarly, selective estrogen receptor modulators (SERMs) have been studied for their impacts on BMD and fracture risk. SERMs are compounds that interact with estrogen receptors and, like estrogen replacement, have broad systemic effects. Raloxifene has been widely used for treating osteoporosis, although its effects on BMD are modest, and it appears to only impact vertebral fractures (141, 142). Long-term use of raloxifene also decreased breast cancer risk, but increased risk of thromboembolic events (108, 143–145). Thus, as with estrogen replacement, SERMs are unlikely to be the gold standard treatment option for osteoporosis, but may be particularly beneficial for women with a strong family history of estrogen receptor-positive invasive breast cancer (146).

Along with impacting a range of tissues, estrogen has profound effects on mental health and is a known regulator of the stress response (147–149). Postmenopausal estradiol therapy provides protective effects against stress-induced cognitive effects, particularly working memory (150). Estrogen also positively impacts distribution of serotonin receptors, suggesting a role for estrogen in mood regulation (151, 152). Glover et al. found that low circulating estrogen levels are associated with higher fear-potentiated startle and fear extinction deficits in women with PTSD (153). Therefore, low levels of estrogen may play a role in PTSD by decreasing fear inhibition. Though several studies have demonstrated a positive impact of estrogen on mental health, negative effects of estrogen on brain activity and memory formation have also been observed. Shansky et al. showed that estrogen treatment impacted activity in the medial prefrontal cortex, resulting in increased sensitivity to working-memory impairment caused by pharmacologic and restraint stressors, possibly through regulation of the alpha-2a adrenergic receptor (154). Dysfunction of the medial prefrontal cortex is associated with stress-related disorders, including major depressive disorder and PTSD. Estrogen may also lead to increased intrusive memories, thereby influencing memory of emotionally arousing events (155). Further, estrogen has been shown to play a role in the pathophysiology of migraines, which are linked to depression, anxiety, abuse, and PTSD (156). Thus, estrogen plays a major and complex role in the stress response and may have both positive and negative effects on different areas of the brain. Estrogen's effects on cognition are likely further complicated by age and hormone status of the patient. It is of note that raloxifene does not appear to affect memory or cognition, and, thus, may be a better treatment option than estrogen replacement for women with a history of mental health disorders (145).

Statins

Statins have been prescribed for the treatment of cardiovascular disease for decades, but are just beginning to be investigated for their anabolic impact on bone [reviewed in Ruan et al. (157)]. Statins have been shown to influence bone remodeling through the BMP pathway and may inhibit osteoclast differentiation through increased BMP-2 expression (158). Statins may also regulate the RANK pathway to inhibit osteoclastogenesis. Bone formation may be promoted by statins through inhibition of osteoblast apoptosis mediated by Smad3 deletion via the TGFβ pathway. Currently, simvastatin and atorvastatin have been shown to have clinical efficacy (increased BMD) in the treatment of osteoporosis, while trials with other statins, such as pravastatin and rosuvastatin, failed to meet study primary outcomes of reduced fracture risk [reviewed in Wang et al. (159)]. Statin bioavailability in bone is low and may explain the lack of full efficacy despite the strong role in bone anabolism demonstrated in animal models and basic laboratory studies (160, 161). However, additional studies and efforts to improve bioavailability should be pursued as a result of the promising outcomes of early clinical and basic studies.

Statins may have beneficial effects on depression and anxiety. Simvastatin had an anti-depressant effect in a chronic mild stress

model (162). However, data is conflicting with respect to patient benefit (163, 164). Epidemiological data suggests a potential positive effect, especially as an adjunctive therapy [reviewed in Salagre et al. (165)]. Statins also have anti-inflammatory and anti-oxidant functions, which may be beneficial for both stress-related pathologies and osteoporosis [reviewed in Bedi et al. (166)]. However, their use for treating psychological stress or osteoporosis concurrent with psychological stress requires additional examination.

Strontium Ranelate

Strontium ranelate is a divalent cation, similar to calcium, and can be administered daily in powder form to treat osteoporosis. Although its effects are weak, it is approved in Europe for treatment of osteoporosis in postmenopausal women and in men at high risk of vertebral and hip fractures who cannot use other pharmacological agents, such as bisphosphonates (16). It results in large increases in BMD, but this is partially due to the heavier strontium ions physically replacing calcium ions within the hydroxyapatite. In postmenopausal women with established osteoporosis, 4-year treatment with strontium ranelate reduced incidence of vertebral fractures by ∼40% and non-vertebral fractures by 16%, while hip fractures were found to be reduced only after *post-hoc* analysis of a high-risk patient subgroup (167, 168). While a potentially effective antiresorptive agent, strontium ranelate may be associated with increased risk of cardiovascular events and, thus, patients must be closely monitored (169).

There are minimal studies that have examined the direct effect of strontium ranelate on mental health. However, improved QOL outcomes associated with its use may offer benefit to those experiencing psychological stress. For example, oral administration of strontium ranelate in postmenopausal women with established vertebral osteoporosis resulted in prevention of QOL impairment compared to placebo group, with clear improvement in emotional and physical dimension scores (170). In addition, a 2008 multicenter trial in Russia analyzed the effect of 1-year administration of strontium ranelate on BMD of patients with postmenopausal osteoporosis. It was found that strontium ranelate increased lumbar vertebra BMD, inhibited local tissue-mediated bone resorption markers, and resulted in improved QOL outcomes, with patients reporting better motility, lowered rates of depression, and improved self-assessments (171). While promising, further studies are needed to determine the impacts of strontium ranelate on mental health and whether or not it may serve as a more suitable treatment option for osteoporotic patients with a history of mental health disorder.

Teriparatide

Teriparatide is a recombinant form of PTH, consisting of the bioactive N-terminal 34 amino acids. PTH is involved in regulation of serum calcium levels and is a stimulator of both bone formation and bone resorption. Teriparatide is the only FDA-approved anabolic bone agent for treating osteoporosis, but is, currently, cost-prohibitive (35, 172). Daily or weekly subcutaneous injections of teriparatide were shown to increase both spine and hip BMD (173). Neer et al. demonstrated that a 20 μg/daily dose of teriparatide resulted in ∼70% reduction in vertebral fractures and ∼50% reduction in non-vertebral fractures in women with low BMD and a previous history of vertebral fractures over a 21-month treatment period (174). However, teriparatide did not reduce hip fracture risk. Teriparatide is associated with a number of negative side effects, including nausea, headache, hypercalcemia, and musculoskeletal pain. In addition, benefits of teriparatide are quickly lost after discontinuation, and it is only approved for up to 2 years of use (102). Importantly, it has also been shown that co-therapy with teriparatide and alendronate does not provide advantage over monotherapy (175).

In regard to mental health effects, common symptoms of hyperparathyroidism overlap with those of psychological stress-associated mental health disease, including fatigue, anxiety, insomnia, and depression. The molecular, cellular, and biochemical mechanisms behind the relationship between PTH and mental health are not known. Recently, however, PTH levels were shown to negatively correlate with plasma corticosterone levels after acute restraint stress (176). In addition, a significant reduction in parathyroid hormone receptor 1 (PTHR1) levels in both the kidney and thyroid was observed in rats exposed to chronic (28-day) daily restraint stress. This potential link is supported by clinical data, which demonstrated that teriparatide resulted in increased plasma and urinary cortisol following sustained treatment (6 months-1 year) (177). These studies suggest clinical considerations should be made regarding the potential impact of teriparatide use on cortisol levels in osteoporotic patients with PTSD, depression, or anxiety.

Psychological Stress Treatments

As described above, it is clear that osteoporosis, particularly osteoporotic fracture, and associated treatments may have substantial mental health impacts. Mental health disorders may also, in turn, have significant impact on bone health. Anxiety has been reported to contribute to lower hip BMD (178). Several studies have shown that depression is a predictive factor for osteoporosis and fracture development (179–181). In addition, pharmacological interventions targeted at improving mental health, particularly in patients with major depressive disorder or PTSD diagnoses, may impact bone health. In the subsections below, we describe commonly prescribed medications for PTSD and depression and then review current literature indicating impacts of these agents on bone health.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Selective-serotonin reuptake inhibitors (SSRIs) have become a first-line treatment for patients with moderate to severe depressive disorders, as they are generally considered safe, well-tolerated, and associated with minimal severe side effects (182). SSRIs function by inhibiting serotonin (see section Serotonin) reuptake by the presynaptic neuron, thereby maintaining higher levels of serotonin in the synapse and increasing postsynaptic neurotransmission. As a result of this inhibition, there is a resultant increase in extracellular concentrations of serotonin in both the brain and periphery. In addition, SSRIs are most highly concentrated in the bone marrow, thus raising the concern as to their impacts on bone metabolism (183). Interestingly,

SSRIs appear to exert a temporally regulated dual-effect on bone. Short-term SSRI administration results in elevated systemic serotonin levels, but these levels are reduced by about 50% over a longer treatment period [reviewed in Ducy and Karsenty G (81)]. In a rigorous study by Ortuno et al., fluoxetine was shown to act on bone remodeling via two distinct mechanisms in mice. When used for <3 weeks, fluoxetine acts peripherally to cause anti-resorptive effects by directly impairing osteoclast differentiation and function through a serotonin-reuptake-independent mechanism that is dependent on intracellular Ca^{2+} levels and the transcription factor, Nfatc1. In addition, these effects were reversible, thus ruling out cell death as the reason for the observed anti-resorptive effects. No effect of fluoxetine was observed on osteoblasts. However, when fluoxetine was given to mice for 6 weeks, it triggered a brain serotonin-dependent rise in sympathetic output that increased bone resorption sufficiently to counteract its local anti-resorptive effect, which led to a net effect of impaired bone formation and bone loss. Hypothalamic extracts from mice treated for 6 weeks with fluoxetine showed significantly lower levels of p-CREB, a downstream mediator of serotonin signaling through Htr2c. The study also found that it was possible to neutralize this long-term effect of fluoxetine treatment through co-treatment with the beta-blocker, propranolol, which leaves the localized peripheral effect intact and prevents fluoxetine-induced bone loss (184).

In accordance with these findings, clinical studies illustrate that, with chronic usage of commonly prescribed SSRIs, bone health is negatively impacted. In numerous studies, SSRIs have been found to increase risk for secondary osteoporosis, lower BMD, and increase incidence of both hip and vertebral fractures (185–192). The direct mechanisms by which SSRIs impact bone health, particularly in humans, are still not wholly understood, particularly due to temporal and location-specific effects of serotonin. However, a promising potential treatment option may be LP533401, an inhibitor of Tph1, that does not cross the blood-brain barrier, thus will not affect synthesis of brain serotonin. LP533401 has been shown in a Phase II clinical trial to not exhibit significant toxicity or side effects in patients being treated for irritable bowel syndrome (193). In rats, LP533401 administration once daily by oral gavage for up to 6 weeks resulted in full rescue of osteoporosis in ovariectomized rodents in a dose-dependent manner (194, 195). Taken together, these studies would suggest that it is important to consider a patient's history of SSRI use when treating osteoporosis, as any benefit received from an osteoporotic drug, such as a bisphosphonate, could be countered by concurrent SSRI use [reviewed in Haney et al. (196)].

Benzodiazepines (anxiolytics)

Benzodiazepines are another commonly prescribed treatment for psychological stress, especially as a second-line or adjunctive medication. These drugs enhance the signaling of the neurotransmitter, gamma-Aminobutyric acid (GABA), through GABA receptors, and may also increase dopamine signaling to reduce anxiety that is often associated with stress. Benzodiazepines are central nervous system depressants and, thus, have sedating effects.

Benzodiazepines have been shown to have significant negative impact on bone health, primarily due to increased fall risk (197). Benzodiazepines have also been shown to decrease osteoblast differentiation through benzodiazepine-like receptors. BMD may also be reduced as a result of benzodiazepine treatment, and their use has been associated with increased ALP, reduced serum levels of vitamin D [reviewed in Fan et al. (198)], and increased levels of prolactin, which, in turn, results in decreased estrogen (199). These studies strongly suggest that benzodiazepines be prescribed with caution among those at risk for development of osteoporosis, and lifestyle modifications and supplementation as adjunctive therapies warrant consideration in these patients.

Barbiturates

Barbiturates, derived from barbituric acid, are a class of central nervous system depressants and are classified as anti-epileptic drugs. Barbiturates are GABA receptor agonists, exerting their effect by blocking transmembrane receptors for the primary excitatory neurotransmitter in the central nervous system, glutamate. The resulting activation of inhibitory GABA signaling coupled with inhibition of excitatory neurotransmitters causes sedation. These drugs are highly addictive and do not have a reversal agent in the case of overdose. Therefore, barbiturates are not as widely prescribed today as they have been in the past. However, these drugs are still prescribed for treatment of anxiety, seizures, migraine headaches, and in the elderly as sleep aids.

Barbiturates are detrimental to bone due to impacts on calcium and vitamin D metabolism and absorption. Although the negative effects of barbiturates are likely multifactorial and complex (200), perhaps the most recognized mechanism is through increased cytochrome p-450 enzymatic activity, which results in production of an inactive form of vitamin D, thereby leading to a reduction in calcium absorption from the gastrointestinal tract. Reduced vitamin D and calcium levels stimulate production of PTH and perpetuate bone loss due to calcium resorption from bone (201, 202). Due to their significant effects on bone resorption, use of barbiturates has been noted as a cause of secondary osteoporosis. As with other CNS depressants, barbiturate use is associated with increased risk of fracture due to an increased fall risk resulting from gait disturbances. Thus, due both to the risk of addiction and implication in osteoporosis, as well as elevated fracture and fall risk, alternatives to barbiturates for the treatment of psychological stress may be preferred.

Beta-Blockers

Beta-blockers act to inhibit β-adrenergic signaling and are commonly prescribed for the treatment of hypertension. More recently, beta-blockers, such as propranolol, have been prescribed for other conditions, including anxiety. The use of beta-blockers for PTSD has also been suggested, with the goal of preventing detrimental memory relapse of traumatic events [reviewed in Roque (203), Burbiel (204)]. However, due to concerns regarding potential negative impact on depression, these medications are not necessarily considered front-line treatments for psychological stress-associated mental health disease.

Given the impact of catecholamines on bone health (discussed above), it is not surprising that beta-blockers may have beneficial

impacts on osteoporosis (205) and have been shown to reduce fracture risk by as much as 50%. In a study of men over the age of 55, long-term (> 5 years) beta-blocker use was associated with increased maxillary BMD compared to those on calcium channel blockers for hypertension (206). In a U.K. study, beta-blocker treatment was associated with reduced fracture risk (207). This was also demonstrated in an Australian study, in which women on beta-blockers were shown to have decreased fracture risk and increased BMD of the hip and ultradistal forearm (208). *In vitro* studies suggest that the positive impact of beta-blockers on bone health may be due to promotion of bone formation by osteoblasts, increased osteoblast numbers, decreased osteoclast numbers, and impairment of osteoclast-mediated bone resorption (209).

LIFESTYLE MODIFICATION AND DIETARY SUPPLEMENTS

In this section, we provide a perspective outlook on lifestyle modifications and dietary supplements that may have beneficial effects on bone health (210) and may reduce psychological stress (211). For example, it has been suggested that the Mediterranean diet may have positive impacts on bone health, whereas the modern Western diet causes a state of low-grade chronic inflammation that promotes osteoporosis (212–214). A movement toward complimentary, alternative and integrative medicine has provided insight into the benefits of adjunctive and naturopathic remedies. Calcium and vitamin D supplementation have well-recognized benefits toward improved bone health and reducing osteopenia. However, their impacts on psychological stress are less well-studied. Other alternative therapies that have been gaining attention include magnesium supplementation and fish oil/omega-3 supplementation. The benefits of exercise in promoting overall health are well-recognized. Recent studies regarding several lifestyle modifications and dietary supplements and their effects on bone health and psychological stress are described below. These alternatives may offer complementary benefit with reduced risk compared to traditional pharmacological intervention, and, therefore, warrant additional study toward potential impact on patient outcome for those with, or at high risk for, osteoporosis and concurrent psychological stress-associated mental health disorders. In the subsections below, literature supporting alternative or adjunctive therapies are discussed. First, the literature indicating effects on bone health are described, followed by a review of the literature indicating impact on mental health.

Exercise

Besides obvious beneficial effects on muscle mass, weight-bearing and resistance exercises can lead to increases in BMD (215). Although this impact may be more beneficial at a young age, some studies have shown that exercise increases BMD in postmenopausal women (216, 217). Longitudinal studies using high-resolution computed tomography scans have shown that regular physical activity improves skeletal microarchitecture (218). Further, exercise and balance can limit fall risk (102). The converse is also true, in that low levels of physical activity are associated with bone loss and >2-fold risk of fracture (219, 220). However, robust data is still lacking on whether there are any beneficial effects of long-term exercise on fracture susceptibility.

It is well-established that regular exercise can improve mental health. Participation in exercise programs has been shown to improve symptoms in patients with anxiety-, stress-, and trauma-related disorders, with positive effects lasting beyond the scope of the training program (221–224). In some cases, exercise therapy was more effective in reducing anxiety than traditional forms of therapy, including psychotherapy and pharmacotherapy (222, 225, 226). The benefits of short- and long-term aerobic exercise on overall mental health and function are multifold. On a biochemical level, exercise has been shown to reverse some of the neurological changes induced by exposure to psychosocial and/or physical stressors, including release of hippocampal corticosterone, decreased neurogenesis, and impaired hippocampal-dependent behaviors, such as learning and memory (227–230). In animal models of stress, both forced and voluntary exercise interventions have been shown to restore neuronal differentiation in the hippocampus (231, 232), increase levels of hippocampal brain-derived neurotrophic factor (BDNF) (233–235), and restore cognitive function (233, 236). There is also evidence that exercise-induced neurochemical changes, including increased production of hippocampal BDNF and altered hippocampal glucocorticoid receptor levels, may be protective against the stress response (237–239). On a psychological level, exercise may act as an interoceptive exposure (240, 241), in which patients with PTSD and anxiety-related disorders are sensitized to feared somatic sensations (242, 243). Alternatively, exercise may produce its anxiolytic effect by offering a distraction from distressing thoughts (244, 245) and/or inducing neurochemical changes, such as increased endorphin production (246). The biochemical mechanisms by which exercise alleviates symptoms in patients with anxiety and PTSD have not been fully elucidated and require further investigation.

Calcium and Vitamin D

Nutrition and intake of appropriate levels of vitamins and minerals play a key role in maintenance of a healthy skeleton. In regard to osteoporosis, calcium and vitamin D supplementation have been the most studied to date. The Women's Health Initiative conducted a large randomized trial involving more than 36,000 postmenopausal women to determine the efficacy of 1,000 mg of calcium combined with 400 IU of vitamin D supplementation daily. It was found that this combination did not significantly impact risk of hip fracture, although *post-hoc* analysis demonstrated benefits for women age 60 years of age or older and those who adhered most strictly to the treatment schedule (247). In contrast, a 2016 meta-analysis of randomized controlled trials found a significant 15% reduced risk of total fractures and a 30% reduced risk of hip fractures with calcium and vitamin D supplementation (248). However, there has been no evidence, to date, that vitamin D supplementation alone reduces fracture risk, although it may reduce fall risk (249). Effects of supplemental calcium alone on fracture risk

are still unknown, as no large-scale, randomized trials have been conducted (102). In addition, vitamin D and calcium supplementation were, not surprisingly, shown to increase risk of kidney stone development by 17% (247). Thus, at this time, vitamin D and/or calcium supplementation alone is not considered an appropriate treatment for osteoporosis.

In regard to mental health, several studies have examined the effects of vitamin D and calcium. Vitamin D is known to play a role in depression (250–252), and vitamin D receptors are present in multiple brain regions (253). Further, recent studies have begun to demonstrate a relationship between anxiety and serum levels of vitamin D (254). This may impact quality of life, particularly in postmenopausal women at increased risk of osteoporosis (255, 256). Vitamin D has also been shown to increase synthesis of neurotransmitters, including dopamine and norepinephrine, in rats (257). However, in a large-scale randomized, double-blinded US trial, no relationship was found between vitamin D/calcium supplementation and depression in over 36,000 postmenopausal women (258). In contrast, a Norwegian randomized, double-blind controlled trial found that weekly administration of vitamin D for 1 year in normal, healthy adults resulted in improved scores for depression compared to placebo (259). In a Korean study, low-dietary calcium was found to be associated with increased depression in middle-aged women (260). In women with premenstrual syndrome, supplementation with 500 mg of calcium carbonate twice daily for 3 months resulted in improvements in parameters assessing early tiredness, appetite changes, and depressive symptoms (261). There are also studies to suggest that calcium supplementation can be used to mitigate symptoms of postpartum depression (262). Thus, there is accumulating evidence of the beneficial effects of vitamin D and/or calcium supplementation on depression.

Magnesium

Magnesium is the fourth most abundant cation in the body and is involved in cardiovascular, bone, and brain health, as well as maintenance of homeostasis (263, 264). Supplementation with magnesium is generally well-tolerated with limited side effects. For bone, magnesium supplementation has been less well studied than calcium and/or vitamin D. However, bones store approximately 60% of total body magnesium, and its release is dependent upon bone resorption (265). In rats, it has been shown that decreased dietary magnesium leads to a reduction in vitamin D, ALP, and OCN levels, as well as decreased bone volume and trabecular thickness (266). Tucker et al. demonstrated that magnesium intake was associated with increased BMD at one hip site for men and women and in the forearms of men (267). In a 2014 Women's Health Initiative study, it was found that postmenopausal women who consumed $>$422.5 mg of magnesium had slightly higher (2–3%) BMD than women who consumed $<$206.5 mg of magnesium daily. In addition, magnesium consumption correlated with increased physical activity, but also increased fall risk (268). A 2017 study demonstrated that dietary magnesium intake led to a 27% decrease in fracture risk (269). Thus, maintaining appropriate levels of magnesium appears to be beneficial in the maintenance of bone integrity.

Magnesium supplementation has been suggested for its anxiolytic effects and has shown promising results in clinical studies. However, additional examination is required to develop appropriate treatment recommendations [reviewed in Boyle et al. (270)]. Low magnesium intake (271) and low serum levels of magnesium have been associated with depression [reviewed in You et al. (272)]. Several studies have also demonstrated positive effects of magnesium supplementation for depression (273, 274). Magnesium has also been used to improve sleep, especially among those with magnesium deficiency. Mechanistic studies of magnesium supplementation on depression have been limited. However, in a model of chronic mild stress, it was demonstrated that magnesium may exert its anxiolytic and anti-depressive effects in part by acting as a GABA agonist and as an inhibitor of N-methy-D-aspartate receptor (NMDAR) (275). Based on these positive effects on mental health and bone integrity, as well as limited negative side effects, magnesium supplementation may serve as a beneficial supplement for osteoporotic patients with a history of mental health disorder.

Omega-3 Fatty Acids

Polyunsaturated fatty acids, including eicosapantaenoic acid (EPA) and docosahexaenoic acid (DHA), are commonly contained in fish oil supplements and fatty fish, such as salmon, tuna, mackerel, and sardines. The ratio of these fatty acids varies across fish oil supplements and can have significant impact on effect and balance of these omega-3 and omega-6 fatty acids in the body. This balance is critical toward the beneficial anti-inflammatory effects of fatty acid supplementation. Due to these anti-inflammatory effects, there have been a handful of studies examining the impacts of fatty acids on bone health [reviewed in El-Sayed and Ibrahim (276)]. Using bone marrow-derived macrophages, Kim et al. demonstrated that DHA led to suppression of macrophage colony-stimulating factor (M-CSF)-induced proliferation of osteoclast precursors. This effect was likely mediated through decreased Akt activation and downregulated cyclin D1 and D2 expression. In addition, DHA led to increased apoptosis in mature osteoclasts (277). In rats, a diet supplemented with chia seeds, which are fatty acid-rich, was shown to increase BMD in the tibia (278). Lavado-Garcia et al. observed a similar effect, with long-chain omega-3 polyunsaturated fatty acid intake contributing to an increase in BMDs in the hips and lumbar spine of normal and osteopenic, but not osteoporotic, Spanish women (279). In a randomized, double-blind, placebo-controlled trial, Dong et al. reported that omega-3 polyunsaturated fatty acid supplementation led to decreased bone turnover by decreasing serum levels of bone-specific ALP and OCN over time (280). However, it was stated that higher doses and a longer duration needed to be tested before a definitive statement could be made as to the effects of fatty acids on bone metabolism. In a systemic review and meta-analysis, Shen et al. suggest that the primary impact of omega-3 fatty acids on bone is a reduction in serum OCN (281). However, there is still a lack in mechanistic understanding of how omega-3 fatty acids may be mediating these effects on bone, particularly

since even just one fatty acid can trigger multiple independent pathways (282).

Depression and anxiety have been associated with reduced levels of polyunsaturated fatty acids (283, 284). Accordingly, several studies have demonstrated a positive effect of fatty acid supplementation [reviewed in Burhani and Rasenick (285)]. One study in rats comparing the effects of EPA and DHA supplementation demonstrated increased anxiolytic effects of EPA (286). Another study demonstrated anti-depressant effects of fish oil supplementation in rats subjected to chronic unpredictable mild stress (287). Fish oil supplementation may also improve the physiological symptoms of psychological stress. Fish oil supplementation has been shown to reduce the effects of mental stress (serial subtraction exercises) on heart rate, calf vascular conductance, and muscle sympathetic nerve activity (288). In contrast, a more recent study demonstrated no benefit of EPA supplementation on perceived psychological stress (289). Therefore, while studies have been promising regarding the use of omega-3 supplementation for treatment of psychological stress, including depression, anxiety, and PTSD, continued research is needed to determine the appropriate type of supplementation, dose, and application. Continued mechanistic studies are needed, but, to date, studies have suggested these supplements impart anti-inflammatory action and modification of neurotransmitter signaling through membrane and G-protein mechanisms [reviewed in Burhani and Rasenick (285)]. Overall, studies have shown promising benefit to multiple pathologies without significant negative impact. As such, fatty acid supplementation may warrant recommendation for concurrent osteoporosis and psychological stress.

CONCLUSIONS

Together, the studies reviewed above suggest that, while osteoporosis and psychological stress occur via differing mechanisms, there are several potential molecular links that exist between a pathological response to stress and the development of bone disease. Although not a comprehensive list, these may include dysregulation of the HPA-axis and SAM pathway, inflammatory pathways, IGF signaling, estrogen, serotonin, GABA, and RANKL (**Figures 1**, **2**). Consequently, an in-depth understanding of the mechanisms that regulate and intersect stress and bone health is needed to determine risk and treatment recommendations.

In addition, the pharmacological therapies used for mental health disorders and osteoporosis may have interacting effects (**Table 1**) that should be carefully considered in making treatment recommendations toward the most beneficial effect. These interactions are likely highly complex and influenced by a number of patient-specific risk factors, including lifestyle, genetics, epigenetics, and diet. Thus, there is a need for further basic and clinical research to determine the significance of chronic psychological stress on bone health. The multifactorial nature of diseases in treatment, lifestyle recommendations, in terms of making informed personalized medicine decisions should also be considered. Alternative or adjunctive therapies, such as lifestyle modification and dietary supplementation, may represent a novel approach to mitigating the effect of concurrent chronic psychological stress and osteoporosis, but further study is needed to examine the potential benefit of these options in this context. Overall, the interaction of psychological stress and osteoporosis is an important example of the need for additional research examining the broad, whole-health effects of chronic psychological stress on disease and the need for further study of the application of lifestyle modifications toward a personalized medicine approach.

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RK and LM: conception and design, drafting, and revising of the manuscript. NJ, SS, and AL: drafting and revising of the manuscript. All authors read and approved the final manuscript.

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Intolerance of Uncertainty and Anxiety-Related Dispositions Predict Pain During Upper Endoscopy

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Although sedatives can defuse anxiety and relieve pain, Esophagogastroduodenoscopy (EGD) still is uncomfortable and threatening for some patients. Identifying patients who tolerate digestive endoscopy less well remains difficult. Using a prospective design and a multimodal assessment of pain, the present study evaluated how anxiety-related variables predicted subsequent pain outcomes. Sixty-two consecutive patients referred for elective EGD were assessed for intolerance of uncertainty (IU), procedure-related worries, anxiety sensitivity and health distress before endoscopy. During endoscopy, a doctor rated patients' pain behavior. After complete recovery from sedation, the patients retrospectively rated endoscopy pain and situation specific catastrophizing thoughts. Descriptive analyses showed that patients undergoing EGD for the first time were more distressed and anxious than patients accustomed to the procedure and needed a higher sedative dose. Notwithstanding sedation, the behavioral rating of pain was above the cut-off value for probable pain for more than half of the patients. IU assessed before endoscopy predicted situational pain catastrophizing (PC) and self-reported pain after endoscopy through procedure related worries. Situational PC not only mediated the effect of worry, but also female gender and younger age were associated with self-reported pain through increased catastrophizing thoughts. Health distress and anxiety sensitivity predicted PC only for women, younger patients, and those not accustomed to the procedure. Our study showed that psychological preparation before sedation is needed especially for first-timers, women, and younger patients, addressing maladaptive cognitive beliefs and acquainting patients with the somatic sensations that they might experience during the procedure.

Keywords: intolerance of uncertainty, anxiety-sensitivity, procedural anxiety, pain catastrophizing, esophagogastroduodenoscopy, prospective-study

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INTRODUCTION

Esophagogastroduodenoscopy (EGD) is a diagnostic procedure carried out using a flexible probe equipped with a camera, which allows the mucous membrane of the esophagus, stomach, and duodenum to be explored visually. The examination lasts a few minutes, is safe, and has many benefits, such as accurate diagnosis and guidance on effective interventions

for upper gastrointestinal conditions. Although EGD is well tolerated, the patients may experience mild to moderate discomfort, and the prospect of inserting the probe through the oral cavity, then sliding it into the stomach, may evoke fears such as that of unpleasant physical sensations, adverse diagnostic outcomes (e.g., cancer), and insufficient sedation (Brandt, 2001). Because of these concerns, the most anxious patients become distressed to the point of preventing EGD from being performed or continued (e.g., Trevisani et al., 2004; El-Hassan et al., 2009; Mitsonis et al., 2011). Moreover, procedural anxiety prevents adherence to diagnostic screening tests, becoming a barrier to the early diagnosis of cancer and other severe chronic conditions (Oikonomidou et al., 2011; Trevisani et al., 2014).

Conscious sedation reduces patient anxiety and discomfort (e.g., Mui et al., 2005) but is not exempt from medical complications, needs additional time and specialized personnel to prepare the patients and monitoring their recovery, and the patients themselves must refrain from activities such as driving and working for hours after EGD. Noteworthy, highly anxious patients are more difficult to sedate and require higher doses to maintain an acceptable level of sedation (e.g., Lee et al., 2004; Bal et al., 2012; Gürbulak et al., 2018). Psychological preparation for EGD is an effective non-pharmacological intervention to defuse pre-procedural anxiety before sedation (Maguire et al., 2004; García Sierra et al., 2013; Kowsalya et al., 2015; Behrouzian et al., 2017; Liu et al., 2018; Ghonaem and Ibrahim, 2019) but can be time-consuming and may cause a delay in the flow of patients, especially if performed routinely the same day of endoscopy (e.g., Behrouzian et al., 2017).

There is a need to prioritize patients who are at greater risk of experiencing clinically relevant anxiety, targeting those to be psychologically prepared according to their needs and personality characteristics. Female gender, younger age, and no previous endoscopy experience are known risk factors for pre-procedural anxiety and low EGD tolerability (Davies and Roy, 2013; Lee et al., 2014; Gürbulak et al., 2018; Sayilan and Oztekin, 2018). However, the psychological characteristics that make these groups more difficult to examine are still unclear, and identifying which patients might tolerate digestive endoscopy less well remains challenging (Hazeldine et al., 2010; Bal et al., 2012). Being almost exclusively focused on anxiety symptoms, previous research has overlooked the role of cognitive characteristics underlying these symptoms (Jones et al., 2004; Essink-Bot et al., 2007; Pontone et al., 2015; Behrouzian et al., 2017). Three of these, IU, anxiety sensitivity, and pain catastrophizing (PC) are worthy of attention.

Intolerance of uncertainty (IU) is a cognitive disposition involved in the emergence and maintenance of anxiety disorders and depression, influencing how people react to uncertain events, however unlikely, appraising them as unfair, unacceptable, and threatening (Carleton et al., 2007a). Worrying is the most direct consequence of IU (Dugas et al., 2005; Shihata et al., 2016). People high on IU tend to engage in a mental simulation about what may or may not occur, erroneously believing that anticipating the feared events might help them to be prepared in case things go awry (De Bruin et al., 2007; Newman et al., 2013). Unfortunately, these thoughts do not entail effective coping strategies, and the feelings of anxiety may persist or even be boosted by worrying rumination (Heiden and Broeke, 2009).

According to Carleton (2016), IU reflects a more basic fear of the unknown "caused by the perceived *absence of information at any level of consciousness*" (p. 5, italics added). This definition is consistent with evidence showing that "first-timers," lacking experiential information about the procedure, tend to feel greater anxiety than "repeaters" (Davies and Roy, 2013) and with studies supporting the effectiveness of psychological preparation, in which the patients are acquainted with the physical sensations that may arise during EGD (Maguire et al., 2004; García Sierra et al., 2013; Behrouzian et al., 2017; Liu et al., 2018; Ghonaem and Ibrahim, 2019).

The fear of pain is among the most prominent causes of anxiety for EGD patients (Brandt, 2001). Different from IU, anxiety sensitivity represents the "fear of arousal-related sensations" that everyone experience in anxiety-inducing situations (Taylor et al., 2007). Although the definition of anxiety sensitivity has recently broadened to include the fear of psychological and social consequences of anxiety (Ebesutani et al., 2013), the construct remains more narrow in scope than IU. This argument prompted Carleton et al. (2007b) to suggest that anxiety sensitivity is likely dependent on IU, which maintains the status of broad transdiagnostic vulnerability factor for a wide range of affective disorders.

Anxiety sensitivity is instead a significant factor for panic disorders and hypochondria (Norton et al., 2005), engendering catastrophic misinterpretations (e.g., a heart attack) of harmless physical sensations (e.g., shallow breathing, palpitations) associated with hyperarousal (Ohst and Tuschen-Caffier, 2018). According to this definition, EGD patients high on anxiety sensitivity, especially those not accustomed with the procedure, might misinterpret the somatic sensations caused by the endoscope as signs of an imminent danger (e.g., chocking, having an iatrogenic perforation), panicking about what was going to happen. Moreover, previous research has also shown that anxiety and anxiety sensitivity were reliably associated with a heightened experience of acute and chronic pain (e.g., Ocañez et al., 2010; Catalano et al., 2017).

Pain catastrophizing (PC) is a third cognitive construct that might be involved in the relationship between procedural anxiety and EGD tolerability. PC is a mindset of exaggerated negative cognitions and emotional schemas that describe people's beliefs, appraisals and feelings related to actual or expected pain experience (Quartana et al., 2009). As a multidimensional construct, PC encompasses ruminative thoughts about pain and failure to defuse them, perceived inability to cope with painful situations, and amplification of pain or fear of the negative consequences of pain (Sullivan et al., 1995). These characteristics resonate those of anxiety sensitivity, especially regarding the magnification of potentially harmful stimuli. For instance, Stewart and Asmundson (2006) maintained that patients high on anxiety sensitivity might be more apt to make catastrophic thoughts about pain when confronted with noxious stimuli, a claim supported by several empirical studies (for a review see Olthuis and Asmundson, 2019).

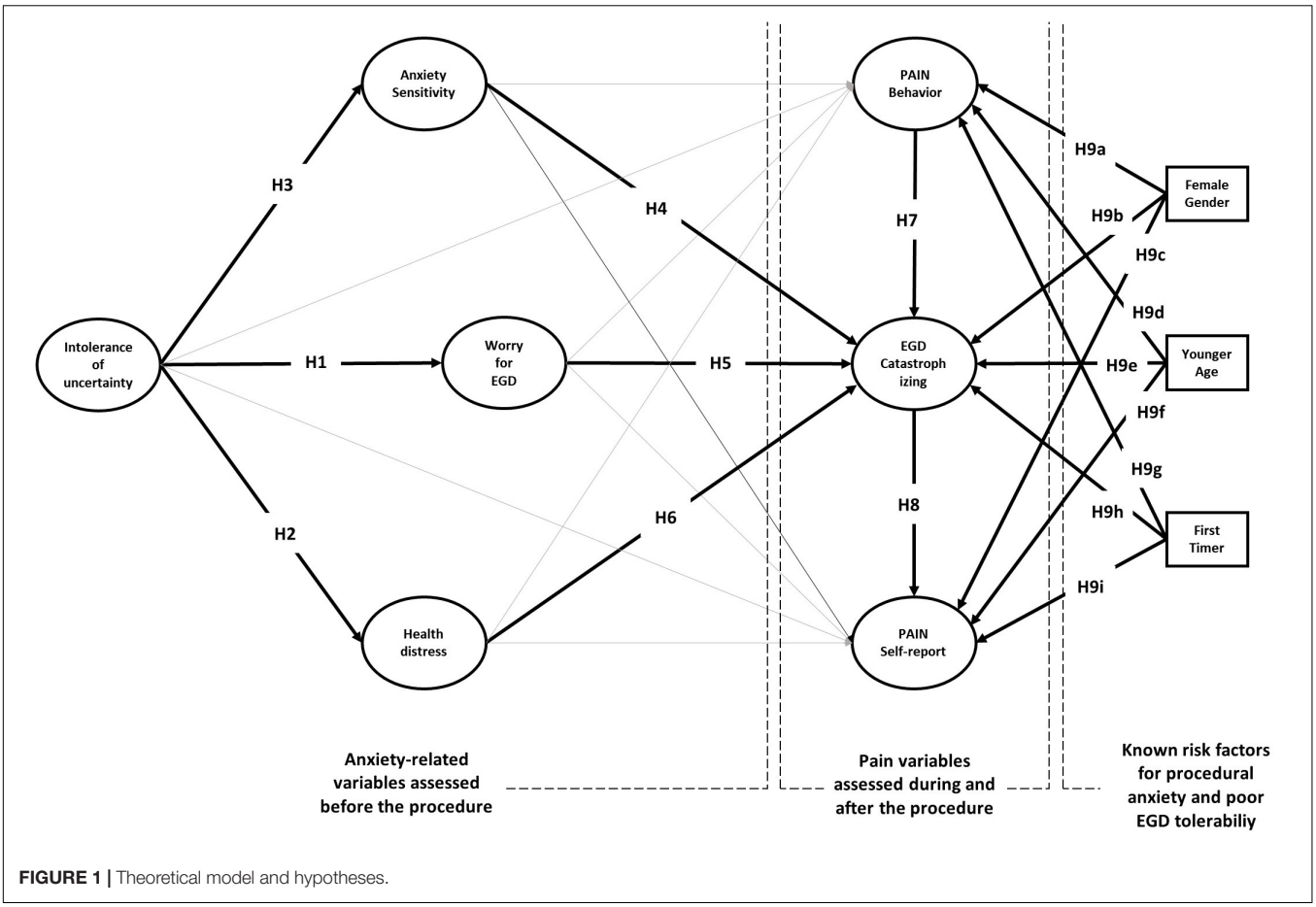

FIGURE 1 | Theoretical model and hypotheses.

Similar to IU and anxiety sensitivity, PC has long been considered a dispositional trait involved in the maintenance of chronic pain and disability (Quartana et al., 2009). However, research has shown that PC has the characteristics of a situational variable, yielding more robust correlations with pain outcomes than dispositional PC for acute pain and experimentally induced stimulation (Strulov et al., 2007; Campbell et al., 2010; Grosen et al., 2016). Because an EGD is more alike to a "clinical experiment" than to a chronic condition, we believe that situational PC has a greater potential to reveal sound relationships with EGD tolerability than dispositional PC.

How IU, anxiety sensitivity and PC shape patient's experience of EGD? Previous research has overlooked the role of these cognitive characteristics. Moreover, no single study has assessed IU, anxiety sensitivity and PC in EGD patients, nor has examined the predictive role of psychological variables using a two-stage prospective design. As shown in **Figure 1**, we assessed IU, anxiety sensitivity, procedure-related worry and health distress before the procedure, observed pain behavior during the procedure, and collected pain perceptions and situation-specific catastrophizing thoughts after the procedure (for details see section Materials and Methods).

Because IU is known to lead to excessive preoccupation, we hypothesized a direct relationship of this variable with EGD worries (H1). According to the transdiagnostic hypothesis, we also expected IU to be linked with patient's health-distress (H2), operatively defined as a combination of depression and anxiety feelings before the procedure. Because IU entails a more general fear of the unknown than anxiety sensitivity, we also hypothesized that the greater the fear of the unknown, the greater the fear of the unknown consequences of procedure-related anxiety (H3). According to H4–H6, we expect that the set of cognitive variables can predict situation-specific catastrophizing thoughts reported by the patients after the procedure. PC has a central role in our model. We expect situation specific catastrophizing thoughts to magnify the experience of pain during the EGD (H7) and lead to greater pain reporting after EGD (H8).

The model also considers female gender, younger age, and no previous endoscopy experience as external sources that can predict the intensity of pain and PC (H9a-i). Adding these variables to the model has several advantages. First, it allows for controlling the effects of known risk factors for pre-procedural anxiety and poor EGD tolerability. Second, it allows studying their moderation effects on the relationships between psychological and pain variables. Moderation effects in a predictive model test "under which circumstances" or "for whom," an independent variable is more (or less) strongly associated with the outcomes. For instance, if the moderation effect of gender on the relationship between anxiety sensitivity

and PC turns out statistically significant, that entails anxiety sensitivity to be differently predictive of PC for men and women.

MATERIALS AND METHODS

Participants

Inclusion criteria for the study were age over 18 years and knowledge of the Italian language. Exclusion criteria were a history of psychiatric disorders, use of antidepressants, adrenoreceptor antagonists, or opioids, current or recent chronic pain syndrome. Eighty consecutive outpatients referred for EGD at the Endoscopy Unit of "Sapienza" University of Rome were eligible for the present study. Seven patients refused to participate (9%). Five (6%) and two (3%) patients did not complete the psychological scales before endoscopy and refused to answer pain questions after endoscopy, respectively. Four patients (5%) were excluded because of a history of psychiatric disorders or current use of medications.

The analyses were carried out on 62 patients (31 women and 31 men), 35 (54%) of which had previous EGD experience. The mean age of the sample ranged from 25 to 86 years (M = 58.24; SD = 14.88). Of the 62 patients referred for EGD, only five patients had signs of serious diseases (e.g., unexplained weight loss, anemia, and fecal occult blood). The remaining 57 patients were either symptomatic (n = 43; e.g., epigastric pain, dyspepsia) or follow-up after surgery (n = 14). The EGD lasted on average 7.43 min (SD = 5.38) and were performed under conscious sedation using a standard endoscope. Patients received a dose of 2–5 mg of midazolam, with a dosage protocol of 0.07 mg/kg. The BMI ranged from 16 to 35 kg/m^2 (M = 24.26; SD = 3.71). Considering the BMI normal range 18–25, one patient was underweight, 24 were overweight, and five were obese (i.e., BMI $>$ 30). The final endoscopic diagnosis was categorized as inflammation (n = 30; i.e., anthropathy, duodenitis, esophagitis), lesion (n = 12; i.e., gastric erosion, polyposis, ulcer, esophageal varicose veins), other conditions (n = 16; e.g., hiatal hernia, Barrett's esophagus), or negative endoscopy (n = 3). Because of an incomplete EGD, the diagnosis was unknown for one patient.

Procedure

Patients were recruited at only one university clinic. Upon arrival, a specializing doctor and a psychologist invited eligible patients to participate in the study. After receiving informed consent from the patient, the psychologist took the patient to a comfortable room and gave him a confidential questionnaire including measures of trait anxiety and depression, IU, anxiety sensitivity, and worry (see instruments). The psychologist was in the room and assisted the patient upon request. A progressive ticket number was assigned to each patient that had to be delivered to the endoscopist doctor in the operating room. Before endoscopy, the doctor verified the absence of exclusion criteria for the study, transcribed patient's anamnestic data, and then proceeded to the EGD. Only one endoscopist was involved in the study and performed all the exams. During endoscopy, a specializing doctor observed the patients and rated patient's pain and sedation level. The specializing and the endoscopist doctors were blinded to the patient's answers to the psychological scales administered before endoscopy. After complete recovery from sedation, the endoscopist doctor invited the patient to answer questions about pain and situational PC, which were placed with the anamnestic data into a sealed envelope on which the patient's progressive number was transcribed. This study was carried out in accordance with the recommendations of the Code of Ethics for Research in Psychology, Italian Association of Psychology. The protocol was approved by the Ethical Committee of the Department of Dynamic and Clinical Psychology, "Sapienza" University of Rome. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Variables and Instruments

Health Distress

The Hospital Anxiety and Depression Scale (HADS) includes seven items for anxiety and seven for depression symptoms, each rated on a 4-point severity scale. The total score is a valid measure of health distress (Snaith, 2003). In the present study, we used the Italian validated version (Iani et al., 2014). The Cronbach's alpha coefficients were 0.74, 0.60, and 0.75 for anxiety, depression, and the total score, respectively. There is no cut-off for the total score, but a subscale score greater than seven is commonly used for fast screening of medical patients at risk for health anxiety and depression (Stern, 2014).

Intolerance of Uncertainty

The Italian version of the Intolerance of Uncertainty Inventory (IUI-A) is a 10-item scale developed to assess the tendency for a person to consider uncertainties in life to be unacceptable and threatening (Carleton et al., 2010). The items were administered using a 5-point scale (1 = "not at all characteristic of me," 5 = "entirely characteristic of me"). The total score is a valid measure of IU as currently defined (α = 0.94, in this study). The normal range for an Italian community sample is between 9 and 46 (Lauriola et al., 2018).

Anxiety Sensitivity

The ASI-3 Italian version (Ghisi et al., 2016) is an 18-item scale assessing tendency to fear the symptoms of anxiety. Responses are given using a five-point Likert scale. The ASI-3 provides three subscale scores: fear of somatic sensations, fear of loss of cognitive or psychological control, and fear of publicly observable anxiety symptoms. In the present study, we administered only the somatic and cognitive subscales (Cronbach's alpha coefficients were 0.89 and 0.90, respectively). To our knowledge, normal ranges for the subscales are currently unpublished.

Worry Questionnaire

To capture cognitive activity associated with pre-procedural anxiety, we developed a Worry for Medical Procedures Scale (WMPS) by rewording the items of the Penn-State Worry Questionnaire (Hopko et al., 2003) in the context of invasive diagnostic examinations. The WMPS included eight items, four of which described specific concerns about the procedure. Two items described worries about test results, while two items described worries about general health (Cronbach's alpha for the total score was 0.90).

Behavioral Rating of Pain

Because the patient was unable to communicate during EGD, we rated the pain responses during endoscopy using the Pain Assessment in Advanced Dementia Scale (PAINAD; Warden et al., 2003). A medical doctor in the operating room assessed the patient's breathing, negative vocalizations, facial expression, body language, and consolability. A total score was obtained from 0 to 10 with higher scores indicating more severe pain (Cronbach's alpha for the total score was 0.90). A score above two indicates possible pain, while a score above four indicates moderate pain (Zwakhalen et al., 2012).

Self-Assessment of Pain

Pain intensity was assessed using visual-analog, numeric, verbal, and face scales. The Visual Analog Scale (VAS) required the patient to place a mark on a 10 cm long horizontal segment that went from "no pain" to "worst imaginable pain." There were no words on the segment between the two ends. We obtained a continuous score in centimeters, ranging from 0 to 10. The numeric scale asked the patient to evaluate how painful was the procedure using integer numbers from 0 to 10, with higher numbers indicating lower pain intensity. The numeric response scale was intentionally reversed to prevent carryover effect. The score was reversed before the analysis. The verbal scale included five verbal descriptors placed in a ranked order. Very severe, severe, moderate, mild, very mild, and no pain was coded using numbers from 5 to 0, respectively. Last, patients were asked to report the experienced pain selecting from six drawings of facial expressions of pain.

Situational Pain Catastrophizing

To capture catastrophizing thoughts occurring during EGD, we used the same items included in the Italian version of the dispositional PC Scale (Monticone et al., 2012), changing the instructions and rewording the items in the past tense. The patients were asked to refer to thoughts, feelings, and physical sensations experienced during the procedure. Paralleling the standard PCS, we got a total score for situational pain-catastrophizing (13 items, Cronbach's alpha = 0.93) and three subscale scores for pain-helplessness (6 items, Cronbach's alpha = 0.88), pain-rumination (4 items, Cronbach's alpha = 0.89), and pain-magnification, 3 items, Cronbach's alpha = 0.63).

Data Analysis

We performed a partial least squares structural equation modeling analysis (PLS-SEM) using Smart PLS 3 (Ringle et al., 2015). PLS-SEM is a non-parametric path analysis method recommended when the goal of the study is prediction rather than theory testing, and the sample size does not permit using standard SEM (Hair et al., 2017). PLS-SEM makes no assumptions regarding the underlying distribution of the variables, working well with non-normal or highly skewed data (Hair et al., 2017).

The model evaluation comprises two stages: the assessment of the "measurement model," dealing with the relationships between the empirical indicators and the latent variables, and the evaluation of the "structural model", which represents the direct and indirect relationships between latent variables. Four quality criteria determine the adequacy of the measurement model. First, all indicators variables should load on the corresponding latent variables above 0.50 (indicator reliability). Second, the Composite Reliability (CR) of each latent variable should be at least above 0.60, or preferably above 0.70 (construct reliability). Third, the Average Variance Extracted (AVE), measuring the proportion of variance in the indicators that is accounted for by the corresponding latent variable, should be 0.50 or higher (convergent validity). Last, the square roots of the AVE for each latent variable should be larger than the estimated correlations of that latent variable with other variables in the model (discriminant validity).

The evaluation of the structural model is based on how well the model predicted the endogenous variables. First, we examined the determination coefficients (R^2) for the endogenous latent variables. According to Hair et al. (2017), R^2-values of 0.75, 0.50, and 0.25 represent high, moderate, and low thresholds, respectively. The predictive accuracy of the model is also evaluated in terms of cross-validation. For this purpose, a Q^2 cross-validation index is obtained for each endogenous variable using a blindfolding procedure assessing the ability of the model to predict omitted data not used for estimation (Hair et al., 2017). Positive Q^2-values indicate that the model has predictive relevance. The higher is the Q^2, the higher the predictive accuracy of the model. The significance of the direct path coefficients is tested using non-parametric confidence intervals obtained from 5000 bootstrap resampling iterations (Streukens and Leroi-Werelds, 2016). Although the two-tailed test type remains the default option in PLS-SEM, a one-tailed test is suitable for small sample analyses and theoretically sound directional hypotheses (Kock, 2015). Besides evaluating the significance of the path coefficients, it is advised to assess their effect size using the f^2, which is the change in R^2 in an endogenous variable when a specific path is omitted from the model. Following Hair et al. (2017), 0.02, 0.15, and 0.35 represent small, medium, and large effect sizes, respectively.

We hypothesized and specifically tested moderating relationships involving age, gender, and EGD experience with anxiety sensitivity, worry, and health distress on situational PC, self-reported pain, and pain behavior. These relationships were tested adding specific interaction terms to the PLS model depicted in **Figure 1**. Each interaction was obtained as the product of the latent variable score for the predictor (e.g., anxiety sensitivity) times the moderator (e.g., gender) after mean centering both factors. Before running the analyses, we checked for multicollinearity among moderators, a violation of regression assumptions occurring when the interaction terms in the model are such correlated to provide redundant information about the dependent variable. The Variance Inflation Factor (VIF) for each moderator is commonly used to assess multicollinearity problems. Under ideal conditions, the VIF should be less than 3, with VIF values less than 4 (or more leniently 5) deemed acceptable (Garson, 2016). With all 27 product terms in the model, twenty showed a VIF < 3, six had a VIF < 4, and only one was 4.1. Multicollinearity did not appear to be a severe problem in the analyses.

RESULTS

Table 1 reports descriptive statistics for sedation and pain-related variables assessed in the total sample and broken down by gender and endoscopy experience. Regarding sedation, the Ramsey score was between 2 and 3 for 85% of the patients, showing that most of them were awake, cooperative, and responsive to commands during the EGD. To attain an adequate level of sedation the patients needed an average dose of 2.97 mg of Midazolam. However, the patients undergoing EGD for the first time needed a higher dose than patients accustomed to the procedure, while the dose administered to women and men was the same. Because there were no between-group differences in BMI, the administration of a higher dose to first-timers was not due to differences in the body mass of the patients.

Notwithstanding sedation, the behavioral rating of pain score was above the cut-off value for probable pain for 29 patients (53%). No differences were found by gender and EGD experience (**Table 1**). However, the data suggested sizeable individual differences in pain behavior, especially for first-timers and women. After the EGD, women reported more pain than man. First-timers also reported more pain than repeaters. However, the statistical tests attained significance only for the face pain scale. When asked to disclose situation-specific catastrophizing thoughts, women reported more helplessness, rumination, and general catastrophizing scores than men. Similarly, first-timers reported more rumination and general catastrophizing scores than men than experienced patients ($p < 0.05$, one-tailed).

Table 2 reports descriptive statistics for the psychological variables assessed before endoscopy. The IU score was in the normal range and there was no difference by gender or endoscopy experience. Regarding anxiety sensitivity, women obtained significantly higher scores than men. First-timers were significantly more distressed and anxious than patients with previous EGD experience ($ps < 0.05$, one-tailed). Similarly, first-timers referred to be more worried than experienced patients, regarding the procedure and its clinical outcomes ($ps < 0.05$, one-tailed). Women also reported more concerns about the procedure than men ($ps < 0.05$, one-tailed).

Table 3 reports the reliability and validity statistics of latent and observed variables included in the predictive model outlined in **Figure 1**. The composite reliabilities were above the recommended threshold of 0.70 for all the latent variables in the model, ranging from 0.80 to 0.97. The AVE for the latent variables was much above the recommended standard of 0.50. The square roots of the AVE were also higher than the correlations of the latent variables with other latent variables in the model, thus supporting the discriminant validity criterion. Taken together, the analyses of the measurement model showed that the composite and indicator reliability, as well as the convergent and discriminant validity of the latent variables, were good.

Intolerance of uncertainty, anxiety sensitivity, worry, and health distress were highly correlated. But the coefficients were not so large as to suggest an overlap of the constructs. Moreover, each of the psychological variables had specific relationships with the pain variables. IU and worry before EGD were associated with situational PC and self-reported pain after EGD. Health distress was significantly associated with situational PC, only. By contrast, anxiety sensitivity was correlated with all pain variables. The inspection of the correlation coefficients suggested that

TABLE 1 | Sedation and pain variables in the total sample and broken by gender and previous EGD experience.

Variables (range)	Total sample *N* = 62		Men *N* = 31		Women *N* = 31				First-timers *N* = 27		Experienced *N* = 35			
	M	*DS*	*M*	*DS*	*M*	*DS*	*t* (61)	*p*	*M*	*DS*	*M*	*DS*	*t* (61)	*p*
Ramsey sedation score (1–5)	2.84	(0.75)	2.77	(0.76)	2.90	(0.75)	0.67		2.93	(0.68)	2.77	(0.81)	0.80	
Midazolam (mg/l)	2.97	(1.16)	2.84	(1.13)	3.10	(1.19)	0.88		3.41	(0.97)	2.63	(1.19)	2.76	**
BMI (Kg/m^2)	24.28	(3.90)	24.61	(3.37)	23.95	(4.40)	0.67		24.67	(3.90)	23.98	(3.93)	0.69	
PAINAD total (0–13)	1.68	(2.06)	1.48	(2.26)	1.87	(1.86)	0.74		1.89	(2.03)	1.51	(2.11)	0.71	
Breathing (0–2)	0.13	(0.34)	0.12	(0.34)	0.13	(0.33)	0.00		0.15	(0.36)	0.11	(0.32)	0.39	
Negative vocalizations (0–2)	0.34	(0.51)	0.32	(0.54)	0.35	(0.49)	0.25		0.41	(0.50)	0.29	(0.52)	0.93	
Facial expression (0–2)	0.44	(0.53)	0.35	(0.55)	0.52	(0.51)	1.20		0.37	(0.49)	0.49	(0.56)	0.84	
Body language (0–2)	0.44	(0.53)	0.39	(0.56)	0.48	(0.51)	0.71		0.52	(0.51)	0.37	(0.55)	1.08	
Consolability (0–2)	0.34	(0.51)	0.29	(0.53)	0.39	(0.50)	0.74		0.44	(0.51)	0.26	(0.51)	1.45	
Self-report pain total (z-score)	0.00	(1.00)	−0.31	(0.91)	0.31	(1.00)	2.59	*	0.14	(0.95)	−0.11	(1.04)	0.98	
Verbal scale (0–5)	4.09	(3.99)	2.91	(3.03)	5.26	(4.52)	2.41	*	4.30	(4.40)	3.92	(3.71)	0.37	
Visual analog scale (0–100)	1.61	(1.38)	1.26	(1.29)	1.97	(1.40)	2.07	*	1.85	(1.32)	1.43	(1.42)	1.20	
Face scale (0–5)	2.21	(1.16)	1.81	(0.95)	2.61	(1.23)	2.89	**	2.59	(1.15)	1.91	(1.09)	2.36	*
Numeric scale (0–10)	2.48	(2.60)	2.03	(2.66)	2.94	(2.49)	1.38		2.33	(2.29)	2.60	(2.84)	0.40	
Pain catastrophizing (0–36)	8.20	(9.03)	4.93	(6.33)	11.35	(10.17)	2.95	**	10.67	(9.60)	6.24	(8.17)	1.95	†
Pain helplessness (0–13)	0.48	(0.66)	0.22	(0.48)	0.73	(0.72)	3.22	**	0.63	(0.71)	0.35	(0.61)	1.64	
Pain rumination (0–17)	0.87	(0.93)	0.51	(0.66)	1.21	(1.03)	3.11	**	1.13	(1.00)	0.66	(0.83)	1.99	†
Pain magnification (0–8)	0.51	(0.82)	0.53	(0.69)	0.48	(0.94)	0.23		0.63	(0.98)	0.41	(0.67)	1.03	

$^{***}p < 0.001$; $^{**}p < 0.01$; $^{*}p < 0.05$; $^{\dagger}p < 0.05$ (one-tailed test).

TABLE 2 | Psychological variables in the total sample and broken by gender and first-time EGD.

Variables (range)	Total sample N = 62		Men N = 31		Women N = 31				First-timers N = 27		Experienced N = 35			
	M	*DS*	*M*	*DS*	*M*	*DS*	*t* (61)	*p*	*M*	*DS*	*M*	*DS*	*t* (61)	*p*
IU total (10–50)	23.25	(9.64)	22.86	(10.1)	23.63	(9.36)	0.30		24.96	(7.91)	21.81	(10.80)	1.26	
AS total (0–48)	11.93	(9.90)	9.24	(6.76)	14.53	(11.7)	2.11	*	13.44	(9.07)	10.66	(10.51)	1.08	
AS cognitive (0–24)	5.44	(5.29)	3.97	(3.66)	6.87	(6.18)	2.17	*	5.77	(4.62)	5.16	(5.86)	0.45	
AS sens. physical (0–24)	6.01	(6.49)	5.28	(4.21)	7.67	(6.01)	1.76	†	7.67	(5.23)	5.50	(5.23)	1.58	
Health distress (1–28)	11.86	(5.56)	10.90	(5.83)	12.83	(5.19)	1.33		13.33	(5.43)	10.58	(5.43)	1.93	†
Anxiety (0–14)	6.95	(3.49)	6.34	(3.34)	7.55	(3.59)	1.33		7.89	(3.40)	6.13	(3.14)	1.96	†
Depression (0–14)	4.91	(3.23)	4.55	(3.55)	5.28	(2.90)	0.85		6.13	(3.41)	4.45	(3.29)	1.17	
Worry total (1–5)	2.42	(1.03)	2.24	(0.95)	2.60	(1.09)	1.38		2.70	(1.04)	2.19	(0.97)	1.97	†
Worry EGD procedure (1–5)	2.36	(1.16)	2.07	(1.02)	2.63	(1.24)	1.91	†	2.66	(1.22)	2.10	(1.06)	1.87	†
Worry EGD outcomes (1–5)	2.55	(1.20)	2.34	(1.07)	2.75	(1.30)	1.30		2.83	(1.16)	2.31	(1.20)	1.68	†
Worry general health (1–5)	2.43	(1.26)	2.47	(1.35)	2.40	(1.18)	0.20		2.67	(1.33)	2.23	(1.18)	1.32	

****p < 0.001; **p < 0.01; *p < 0.05; †p < 0.05 (one-tailed test).*

TABLE 3 | Reliability and validity of the latent variables.

	AVE	CR	1.	2.	3.	4.	5.	6.	7.	8.	9.	
1. Intolerance of uncertainty	0.94	0.97	0.97***									
2. Anxiety sensitivity	0.87	0.93	0.70***	0.93***								
3. Health distress	0.67	0.80	0.63***	0.60***	0.82***							
4. Worry	0.72	0.88	0.49***	0.45***	0.61***	0.85***						
5. Pain behavior	0.71	0.92	0.16***	0.23***	0.13***	0.16***	0.85***					
6. Self-report pain	0.69	0.90	0.20***	0.20***	0.21***	0.17***	0.56***	0.83***				
7. Pain catastrophizing	0.69	0.87	0.24***	0.36***	0.37***	0.43***	0.53***	0.62***	0.83***			
8. Female gender	1.00	1.00	0.05***	0.26***	0.18***	0.15***	0.08***	0.33***	0.35***	1.00		
9. Experienced patient	1.00	1.00	−0.15****	−0.15***	−0.25***	−0.24***	−0.11***	−0.16***	−0.24***	−0.16***	1.00	
10. Age	1.00	1.00	−0.07****	0.06***	−0.14***	−0.11***	−0.14***	−0.27***	−0.34***	0.00***	0.41***	1.00

****p 0.001; **p 0.01; *p 0.05 (one-tailed test based on 5000 bootstrap replications). Coefficients in the diagonal are the squared root of AVE. Coefficients below the diagonal are correlations among the latent variables in the model. Because gender, age, and endoscopy experience are observed variables, their CR and AVE are by definition equal to 1.00. AVE, Average Variance Extracted; CR, Composite Reliability.*

situational PC seemed to have a pivotal role, being significantly associated with all the psychological variables before EGD, and with the behavioral rating of and self-reported pain, during and after the procedure, respectively. As in previous descriptive analyses, female gender was significantly associated with anxiety sensitivity, while no previous endoscopy experience was related to greater health distress and worry. Older age was also negatively correlated with PC and self-reported pain.

Figure 2 shows the estimated structural model, including the path coefficients and R^2 and Q^2 statistics for the endogenous variables. The model accounted for 49, 39, and 24% (all ps < 0.001) of the variance in anxiety sensitivity, health distress, and EGD-related worry, respectively. IU was significantly associated with anxiety sensitivity ($f^2 = 0.97$), health distress ($f^2 = 0.64$), and worry ($f^2 = 0.32$). The model explained 54% ($p < 0.001$) and 42% ($p < 0.001$) of the variance in situational PC and self-reported pain, respectively. The prediction was not significant for pain behavior during EGD ($R^2 = 0.09$; $p = 0.173$). According to Hair et al. (2017), the effect sizes were large for situational PC and self-reported pain, and small-medium for pain behavior. The Q^2-values were all positive, supporting the robustness of the model in terms of cross-validation.

Different from the correlations reported in **Table 3**, neither anxiety sensitivity nor health distress predicted any of the pain variables after controlling for each other and all the other variables in the model, including age, gender, and EGD experience. Only worry before EGD remained a significant predictor of situational PC ($f^2 = 0.07$). Regarding pain variables, the model showed that pain behavior during EGD predicted situation specific catastrophizing thoughts ($f^2 = 0.34$), which in turn were associated with self-reported pain after EGD ($f^2 = 0.34$). Female gender and patient's age also predicted PC (f^2s = 0.13 and 0.12, respectively). Unexpectedly, the patient's experience with EGD did not predict any of the pain variables. In addition to testing specific path coefficients, the model allowed us to examine several indirect relationships among variables. Situational PC mediated the effect of pain behavior (Indirect effect = 0.25; 95% CI = [0.13, 0.38]; $p = 0.001$), gender (Indirect effect = 0.15; 95% CI = [0.05, 0.29]; $p = 0.021$), age (Indirect effect = −0.16; 95% CI = [−0.06, −0.28]; $p = 0.008$), worry (Indirect effect = 0.14;

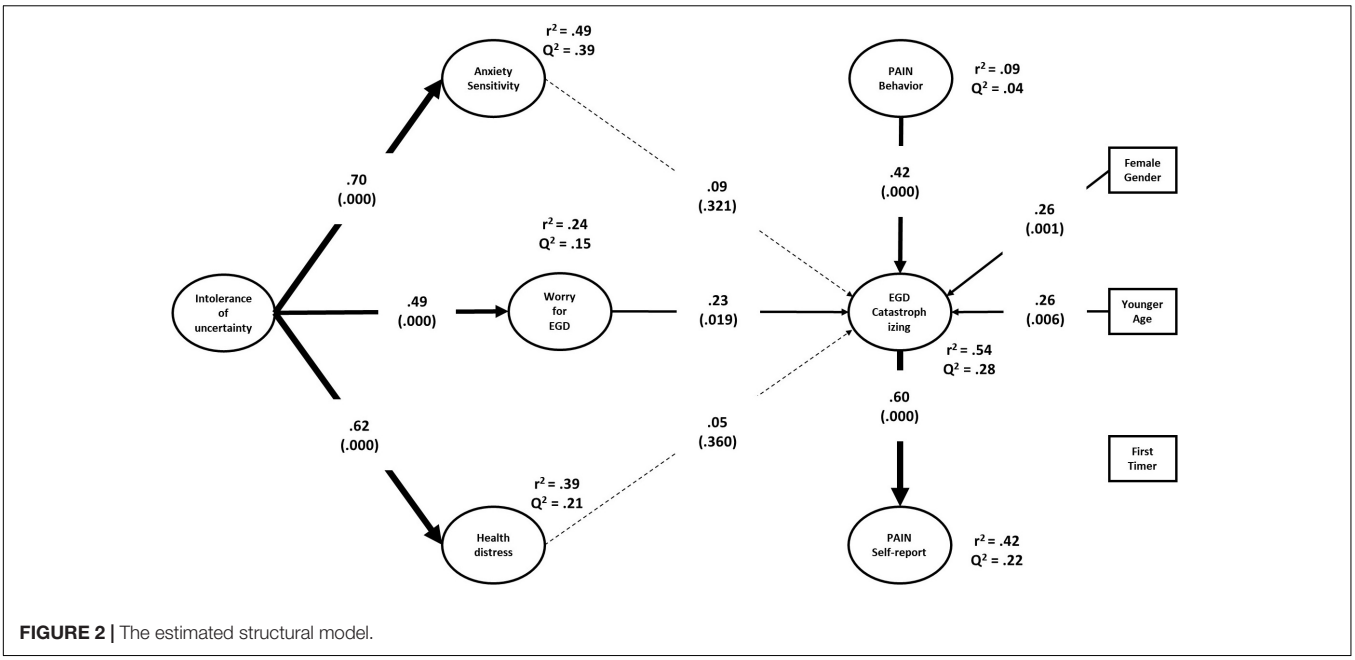

FIGURE 2 | The estimated structural model.

95% CI = [0.03, 0.30]; $p = 0.043$) on self-reported pain. Moreover, worry mediated the effect of IU on situational PC (Indirect effect = 0.11; 95% CI = [0.03, 0.24]; $p = 0.042$).

Younger age and female gender, but not EGD experience, were associated with higher PC. Nevertheless, previous descriptive analyses had shown that first-timer patients tended to be more distressed before EGD and required higher doses to attain acceptable levels of sedation, too. Notwithstanding this, neither anxiety sensitivity nor health distress predicted situational PC. Neither, EGD experience seemed to play any role in the model. It is still entirely possible that the prediction of pain outcomes might depend on the interactive effects of psychological characteristics with age, gender, and EGD experience.

Using the available data, we tested specific hypotheses concerning the role of EGD experience (as well as those of age and gender) as factors that might alter the average level of PC as a function of anxiety sensitivity, worry, and health distress. As one can see from **Table 4**, EGD experience and female gender moderated the prediction of PC by anxiety sensitivity and health distress. Patient's age was also a significant moderating factor in all of the predictive relationships mentioned above. By contrast, no moderation effects were detected for pain-behavior and self-reported pain as dependent variables, which remained not such greatly affected from the psychological status of the patients before EGD (except the indirect effect of worry on self-reported pain).

Because a moderation effect could be very informative about "under which circumstances" or "for whom," an independent variable is more (or less) strongly associated with the outcomes, we examined the simple slopes for situational PC on the three independent variables for men and women, first-timers and repeaters, and younger and older patients. As one can see from **Figure 3**, PC significantly increased with anxiety sensitivity, worry, and health distress, but only for younger patients. Likewise, anxiety sensitivity and health distress significantly predicted situational PC thoughts, but only for first-time patients and women.

DISCUSSION

Being focused on anxiety symptoms, previous research has overlooked the role of their cognitive antecedents, which lead patients to experience overwhelming anxiety before EGD, misinterpret uncomfortable physical sensations, and increase the risks and the costs associated with over-sedation (Jones et al., 2004; Essink-Bot et al., 2007; Pontone et al., 2015; Behrouzian et al., 2017). Using a two-stage prospective design, the present study adds to the extant literature showing that IU, anxiety sensitivity, health distress, and worry are associated with subsequent clinical outcomes in the pain domain. Each of the four cognitive variables assessed before endoscopy had a specific predictive relationship with PC, self-reported pain, and behavioral pain ratings assessed after and during EGD, respectively.

First of all, our study showed that IU assessed before endoscopy was associated with situational PC and self-reported pain after endoscopy. Paralleling previous research on anxiety disorders (Dugas et al., 2005; Shihata et al., 2016), our multivariate analysis showed that IU prompted specific EGD-related worries, which in turn were predictive of pain-catastrophizing and pain. Thus, patients high on IU reacted to the possibility of complications or unfavorable test results, worrying about the negative events that might happen during or after the procedure. In the endoscopy situation, worrying is maladaptive in that it cannot prevent any of the feared negative events from occurring (De Bruin et al., 2007; Newman et al., 2013). Rather, worrying about the impending procedure led patients to ruminate and

TABLE 4 | Tests of moderation effects.

Effect	Beta	LLCI	ULCI	*t*-value	p	Effect	Beta	LLCI	ULCI	*t*-value	p	Effect	Beta	LLCI	ULCI	*t*-value	p
AS × EXP – > PBR	−0.18	−0.42	0.07	1.15		WO × EXP – > PBR	0.02	−0.19	0.27	0.14		HD × EXP – > PBR	−0.03	−0.30	0.23	0.21	
AS × EXP – > PCS	−0.29	−0.48	−0.10	2.43	**	WO × EXP – > PCS	−0.04	−0.04	0.12	0.22		HD × EXP – > PCS	−0.26	−0.45	−0.07	2.25	*
AS × EXP – > PSR	−0.03	−0.28	0.17	0.22		WO × EXP – > PSR	0.16	−0.02	0.38	1.29		HD × EXP – > PSR	0.00	−0.24	0.22	0.01	
AS × FEM – > PBR	−0.07	−0.36	0.19	0.40		WO × FEM – > PBR	0.03	−0.22	0.27	0.20		HD × FEM – > PBR	0.08	−0.23	0.36	0.44	
AS × FEM – > PCS	0.22	0.05	0.41	1.98	*	WO × FEM – > PCS	0.07	−0.13	0.23	0.67		HD × FEM – > PCS	0.22	0.05	0.41	1.98	*
AS × FEM – > PSR	0.10	−0.15	0.33	0.70		WO × FEM – > PSR	0.03	−0.20	0.27	0.23		HD × FEM – > PSR	0.14	−0.06	0.38	0.99	
AS × AGE – > PBR	−0.03	−0.23	0.21	0.20		WO × AGE – > PBR	−0.08	−0.30	0.19	0.54		HD × AGE – > PBR	0.00	−0.24	0.28	0.00	
AS × AGE – > PCS	−0.41	−0.62	−0.26	3.76	***	WO × AGE – > PCS	−0.37	−0.57	−0.15	2.77	**	HD × AGE – > PCS	−0.29	−0.45	−0.07	2.31	*
AS × AGE– > PSR	−0.11	−0.30	0.08	0.91		WO × AGE – > PSR	−0.04	−0.25	0.17	0.29		HD × AGE – > PSR	−0.18	−0.39	0.04	1.26	

****p < 0.001; **p < 0.01; *p < 0.05 (one-tailed test based on 5000 bootstrap replications). AS, anxiety sensitivity; EXP, previous EGD experience; FEM, female gender; AGE, patient's age; WO, worry; HD, health distress; PBR, pain, behavioral rating; PSR, pain, self-report; PCS, pain catastrophizing. LLCI, 95% Lower Limit Confidence Interval; ULCI, 95% Upper Limit Confidence Interval.*

catastrophize about unpleasant physical sensations, which in turn increased the likelihood of tolerating EGD less well.

A second major finding of the study was that situational PC had a pivotal role in the chain of events that lead to low tolerability. Not only it mediated the effect of worry, but also female gender and younger age were both associated with self-reported pain through increased catastrophizing thoughts. Foreshadowing the discussion of the clinical implications, it looks like that PC thoughts during endoscopy were likely responsible for low tolerability for these specific groups of patients (Davies and Roy, 2013; Lee et al., 2014; Gürbulak et al., 2018; Sayilan and Oztekin, 2018). Our findings add to extant literature showing that situational PC has sound relationships with the patient's perceived pain, as also shown by studies of patients undergoing other invasive medical procedures or surgery (Strulov et al., 2007; Campbell et al., 2010; Khan et al., 2011; Pinto et al., 2012; Grosen et al., 2016).

Patient's health distress and anxiety sensitivity were significantly associated with situational PC in bivariate analyses. Also, anxiety sensitivity was correlated with evident pain behaviors during endoscopy. However, subsequent analyses showed that these correlations did not yield significant regression paths in multivariate analyses. Different from worry, the prediction of PC by health distress and anxiety sensitivity was moderated by the other known risk factors for low tolerability. In particular, the two anxiety-related variables affected subsequent catastrophizing thoughts only for women, younger patients, and those not accustomed to the procedure. These findings corroborate previous research aimed at identifying which patients tolerate digestive endoscopy less well (Davies and Roy, 2013; Lee et al., 2014; Gürbulak et al., 2018; Sayilan and Oztekin, 2018) and suggested that addressing health distress and anxiety sensitivity is of utmost importance to make these groups of patients more compliant and easy to examine (Hazeldine et al., 2010; Bal et al., 2012).

The lack of information about what might happen during a medical procedure is an important distressing factor, able to activate cognitive distortions in the appraisal of threat (Dugas et al., 2005; Shihata et al., 2016). In keeping with this view, we hypothesized first-timers to be more distressed and worried before endoscopy, as also noticed in a previous study (Davies and Roy, 2013). This hypothesis was supported in the present study, too. Noteworthy, first-timers also needed higher Midazolam doses than more experienced patients. Because first-timers did not differ from repeaters in the average BMI, it seems likely that the medical personnel – blinded to the preceding psychological assessment – judged first-timers as ostensibly more agitated before the procedure and opted for administering higher sedative doses to. After all, previous research had already shown that the more apprehensive patients are more difficult to sedate (e.g., Lee et al., 2004; Bal et al., 2012; Gürbulak et al., 2018), and our findings are consistent with this view.

Although EGD is typically well tolerated under conscious sedation, our study showed that more than half of the patients were above the cut-off value for probable pain using a behavioral rating scale. Because most patients attained an adequate level of sedation, it is worth asking whether

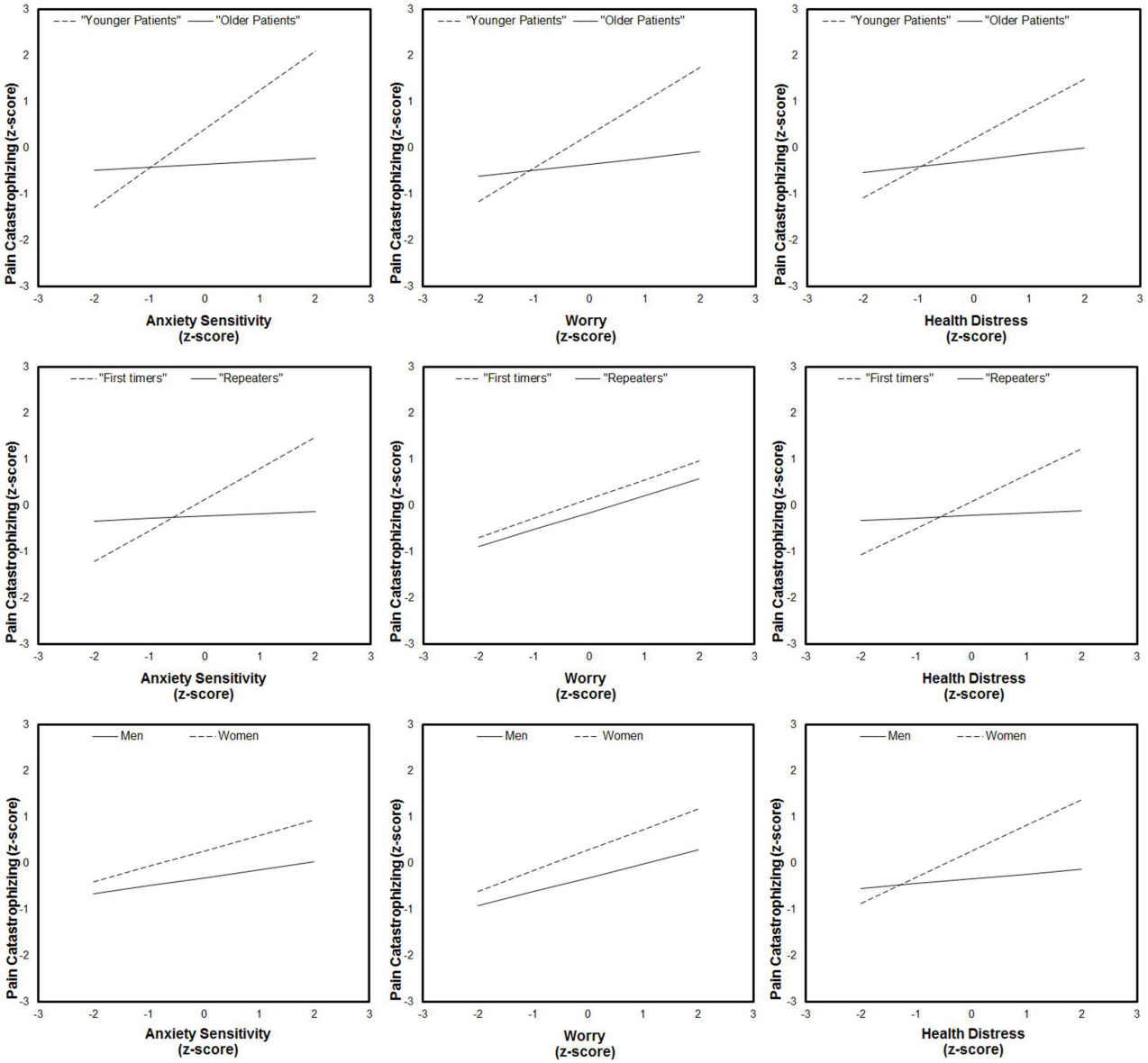

FIGURE 3 | Simple slope analysis.

the patients coped with a "real pain" or just misjudged unpleasant physical sensations as pain (Ocañez et al., 2010). Previous research has shown that psychological preparation for EGD is more effective if the patient is acquainted with the physical sensations that he/she will experience (Maguire et al., 2004; García Sierra et al., 2013; Kowsalya et al., 2015; Behrouzian et al., 2017; Liu et al., 2018; Ghonaem and Ibrahim, 2019). Merely providing information about the procedure can even be counterproductive for some patients (Bytzer et al., 2007).

Before concluding it is worth acknowledging some limitations of the present study. First, the sample size was relatively small. Although the number of patients was adequate for performing non-parametric analyses, it precluded us from controlling other qualitative variables potentially influencing pre-procedural anxiety, like motives for a referral to the endoscopy center or final diagnosis after endoscopy. Second, PC and self-reported pain were both assessed after the procedure. This might threaten the directional interpretation of our findings concerning the prediction of self-reported pain based on a concurrent assessment of PC. Last, we recruited patients at only one university clinic, and only one endoscopist performed all exams. Thus, the findings of the present study should be cautiously interpreted regarding their generalizability to smaller clinics, private diagnostic wards, or less skilled operators.

Its limitations notwithstanding, our study is the first to address the interplay of IU, anxiety sensitivity and PC in relation to EGD tolerability. Moreover, our findings may enable identification

of potential avenues for psychological intervention in the endoscopy setting. While relaxing music or aromatic care have been suggested to defuse procedural anxiety (e.g., Rudin et al., 2007; Hu et al., 2014), these interventions miss the psychological elements highlighted in the present study. Indeed, procedural anxiety is likely to evolve into painful sensations when the patient – especially if young, female, or first-timer – negatively appraises the unusual bodily sensations and the mental events associated with EGD. Accordingly, part of patient preparation should be focused on replacing worries and catastrophic thoughts with more positive appraisals of the medical examination and its results addressing negative beliefs and anticipated emotions. This is typically done in chronic pain using cognitive behavioral therapy that requires weeks before producing appreciable results. A major constraint for psychological interventions in the endoscopy suite is the time needed to produce effective reappraisals. Some studies, however, sound promising. For instance, EGD patients who received psychological preparation 2–3 h prior the endoscopy significantly reduced procedural anxiety through information about endoscopy, cognitive preparation (e.g., positively reframing the situation), and behavioral interventions (e.g., breathing exercising, swallowing training) (Behrouzian et al., 2017). Likewise, a 12 min preparation reduced patient's distress during endoscopy using information about the sensations and sequence of events associated with EGD and behavioral training based on breathing exercises, swallowing technique, and a tongue depressor task (Maguire et al., 2004).

Although promising, none of the studies mentioned above has targeted IU, anxiety sensitivity and PC, nor considered pain as the primary outcome. An avenue for future research could be designing interventions in which patient training is aimed to replace negative beliefs with positive coping self–statements (e.g., "I can handle this, just relax"), that is a recommended strategy to cope with acute pain through psychological preparation (Bruehl and Chung, 2003). Interventions based on a clinical approach to case studies (Langher et al., 2017) could also shed light on whether reducing maladaptive beliefs in first-timers, women, and younger patients lead to corresponding improvements in EGD tolerability as predicted by our model.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

AUTHOR CONTRIBUTIONS

This manuscript updates and extends a preliminary research report presented at the Digestive Disease Week 2018. The final version of this manuscript was written by ML, MT, and SP, who contributed equally to the theoretical and empirical aspects of the study. RP contributed to the collection and analysis of medical data and wrote a preliminary version of this manuscript. GL and AF collected and analyzed the psychological data. CP and MR collected and analyzed the medical data.

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CASE REPORT
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Longitudinal Neuropsychological Assessment in Two Elderly Adults With Attention-Deficit/Hyperactivity Disorder: Case Report

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The neuropsychological deficits in attention-deficit/hyperactivity disorder (ADHD) may present clinical features similar to mild and/or major neurocognitive disorder and may act as a confounding factor, making it difficult to detect cognitive decline. In this paper, we present the results of longitudinal neuropsychological evaluations in two elderly women with ADHD. Three neuropsychological assessments were performed in two women with ADHD (60 and 77 years old) between 2010 and 2013 at intervals varying from 12 to 15 months. We used structural magnetic resonance imaging to rule out significant abnormalities that could account for cognitive impairment. The results showed two different cognitive profiles with fluctuations in performance over these 2 years, sometimes with improvement and sometimes with decline of some functions such as attention, memory, inhibitory control, and reaction time. To minimize confounding aspects of these fluctuations in clinical practice, we used a longer follow-up with the application of a reliable change index and a minimum of three spaced assessments to provide a more consistent baseline cognitive profile. Our findings did not indicate a consistent cognitive decline, suggesting a less pessimistic perspective about cognitive impairments that could be a prodrome of ADHD-related dementia.

Keywords: attention-deficit/hyperactivity disorder, elderly, neuropsychological assessment, cognitive decline, longitudinal evaluation

INTRODUCTION

According to the American Psychiatric Association (American Psychiatric Association [APA], 2013), attention-deficit/hyperactivity disorder (ADHD) is a complex neuropsychiatric disorder with a persistent pattern of inattention and/or hyperactivity–impulsivity throughout the lifetime. The symptoms interfere with development or functionality in multiple areas of life, such as in academia and relationships as well as at work. This disorder occurs in most cultures in approximately 5% of children and 2.5% of adults (American Psychiatric Association [APA], 2013); a prevalence of approximately 3% in older people has been described (Guldberg-Kjär and Johansson, 2009; Michielsen et al., 2012).

Although studies show an age-dependent decline in ADHD symptoms (Michielsen et al., 2012; Das et al., 2014), the persistence of symptoms might also lead to significant impairment in older age with a cumulative impact (Kooij et al., 2016; Srinivasan et al., 2016). Moreover, multiple domains of neurocognitive impairment such as executive function, attention, memory, and language are common in children (Sjöwall et al., 2013, 2015; Martino et al., 2017; Salari et al., 2017; Fabio et al., 2018; Shephard et al., 2018; Sjöwall and Thorell, 2019), adolescents (Fried et al., 2016; Steward et al., 2017; Weyandt et al., 2017), and young adults with ADHD (Faraone et al., 2015; Mostert et al., 2015; Antshel et al., 2016; Salomone et al., 2016). Recent studies suggest that some of these impairments may persist in older adults (Fuermaier et al., 2013; Thorell et al., 2017; Coelho et al., 2018).

There is large variability in cognitive expression among younger individuals and older adults with ADHD compared to healthy controls, ranging in individuals with ADHD from a complete lack of deficient scores to severe impairment (Mostert et al., 2015; Thorell et al., 2017). In addition, psychiatric disorders, such as depression and anxiety, are frequently comorbid with ADHD, which remains true for older adults (Michielsen et al., 2013; Das et al., 2014). The overlapping of symptoms can increase the patients' cognitive difficulties and further complicate the diagnosis of this disorder (Michielsen et al., 2013).

In current psychogeriatric practice, ADHD still goes unrecognized. Existing cognitive deficits may present clinical features similar to mild and/or major neurocognitive disorder and may also act as a confounding factor, although these conditions differ from ADHD by their late onset (American Psychiatric Association [APA], 2013). However, clinicians need to pay extra attention to possible cognitive decline and dementia (Kooij et al., 2016). ADHD shares some similarities with the cognitive changes that come with aging, such as increased attentional vulnerability and less efficient memory (Harada et al., 2013), which may cause increased impairment in daily functioning in older individuals with ADHD (Thorell et al., 2017).

In relation to symptoms across the adult life span, studies have analyzed the association between ADHD and mild cognitive impairment (MCI, currently mNCD) and dementia. Golimstok et al. (2010) found a higher risk of dementia with Lewy bodies in patients with ADHD symptoms prior to adulthood, while a study conducted by Ivanchack et al. (2012) found no association between ADHD and mNCD or dementia. More recently, Fluegge and Fluegge (2018) found an association between antecedent ADHD (severe ADHD phenotype) and dementia subtype risk [Lewy body dementia (LBD) and Alzheimer's disease (AD)]. They suggest that these relationships may be dependent upon the extent of metabolic dysregulation since controlling the analyses for diabetes, the significant association between antecedent ADHD and risk of AD does not remain, but it remains for LBD.

In the elderly population, neuropsychological measures have proven to be important tools to help clinicians identify cognitive and functional profiles that can differentiate the transition from benign cognitive aging to dementia (Fichman et al., 2013). However, due to the factors discussed above regarding ADHD, finding patterns of change that may indicate earlier cognitive decline in older ADHD is a great challenge. Considering the heterogeneity in cognitive expression in patients with ADHD, assessments are a useful tool to verify individual differences and measure changes in cognitive functioning over time, distinguishing changes that may be clinically relevant in patients with ADHD (Lange et al., 2014). Thus, because results from longitudinal studies are not yet available, case reports may initially be more useful for providing preliminary insights and discussion about patterns of cognitive functioning over the long term in this age group that is common in our clinical practice. To our knowledge, there are no prospective studies examining cognitive performance in older adults with ADHD, with or without treatment, evaluated with a comprehensive battery of cognitive tests.

The aim of the present case reports was to investigate the presence of cognitive decline and to identify other neuropsychological characteristics in elderly subjects diagnosed with ADHD.

CASE REPORT

Participants signed a free and informed consent form consenting to participation in the research and publication of the data collected in a case report. The final format of this manuscript along with the authorizations for publication was submitted and approved by the ethics committee of the Hospital das Clínicas of the University of São Paulo, protocol number 3.118.878.

Case 1

Mrs. G.F., 60 years old, married, oceanographer, civil servant. She exhibited behaviors such as inattentiveness and forgetfulness dating back to childhood, when they were associated with poor performance at school to the point where she had to repeat grade 1. In adulthood, she exhibited significant functional impairment due to the inability to self-organize or prioritize tasks, a tendency to procrastinate, and a need for silence to concentrate and be productive. Eventually, she resigned from a management position at work because she was not able to finish assignments on time and had to take work home, which affected her family life. Psychiatric care was initially sought due to a depressive episode with persistence, even after remission, of the following symptoms: inattentiveness, forgetfulness, difficulty falling asleep, delays meeting her commitments, and lack of planning.

Medical History

No family history of dementia and no clinical problems were reported at the first assessment. Neuroimaging exams (MRI) revealed normal morphology and size for the patient's age group. There was no evidence of acute ischemic injury.

Diagnosis

Attention-deficit/hyperactivity disorder (inattentive subtype) and depressive disorder (remitted). The proposed medical treatment was venlafaxine 75 mg/day and methylphenidate up to 60 mg/day.

Case 2

Mrs. T.B, 77 years old, widowed, four completed years of formal schooling, retired. In 2001, she was 67 years old and healthy; however, a friend observed that she was quite absent-minded and advised her to seek help. The patient reported that she was agitated and forgetful during childhood and was the only one of three siblings who failed to complete a higher education. As a child, she was restless, used to escape from school to play, and did not pay attention when she was in the classroom. As a consequence, she often failed school assignments, needed to repeat some school years, and dropped out of school in her early teens. She worked many years for a company where the work was mechanical and repetitive, and she rarely arrived on time at work, missed appointments, and was less efficient than her colleagues. She never read an entire book because of her difficulty concentrating. She always forgot to pay bills, lost or misplaced personal objects, and needed the help of her family to remember commitments. She married at 20, and her husband took care of everything. After he died, her everyday life was seriously affected. Eventually, her children had to assume the task of organizing her life. Some years later, before treatment, she left home forgetting a roast in the oven.

Medical History

At the first assessment, in 2001, the patient reported no clinical problems, no signs of depression or anxiety, and denied having ever experienced any psychiatry conditions. At that assessment, an electrocardiogram (ECG; results were within the limits of normality) and a computerized tomography scan of the brain (presented as preserved, with normal attenuation values to X-rays) were collected.

Diagnosis

Attention-deficit/hyperactivity disorder (inattentive subtype). The proposed medical treatment was methylphenidate up to 10 mg/day. In the period leading up to the last evaluation, she took methylphenidate 20 mg/day.

Procedures

Participants were treated at the hospital by psychiatrists and neuropsychologists of the Attention Deficit Hyperactivity Disorder Program (PRODATH) and followed up for 2 years. The assessment included a complete clinical history and clinical examination. ADHD diagnosis was performed according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (American Psychiatric Association [APA], 2013), criteria, and comorbidities were investigated. Both participants were subjected to structural magnetic resonance imaging (MRI) to rule out significant abnormalities that could account for cognitive impairment and/or act as confounding factors. Laboratory tests and an ECG were also performed. Estimated intellectual quotient (IQ) (Ringe et al., 2002) and Mini-Mental State Examination (MMSE) (Folstein et al., 1983) measures were collected in 2010 during the first neuropsychological evaluation. Responses to the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm, 1994) were collected only at the third assessment. In addition, we used the Geriatric Depression Scale (GDS) (Yesavage et al., 1983) and Beck Anxiety Inventory (BAI) (Beck et al., 1988).

At the time of assessment, the participants were requested to interrupt their medication (methylphenidate) for 24 h, and the Case 1 participant continued use of an antidepressant medication. The participants signed an informed consent form allowing the use of their clinical and neuropsychological data.

Neuropsychological Evaluation

Three neuropsychological assessments were performed from 2010 to 2013 at intervals varying from 12 to 15 months. The ages of the participants refer to age at neuropsychological baseline assessed in 2010. Each assessment comprised two sessions lasting approximately 90 min each. The instruments used in the neuropsychological evaluation can be found in **Table 1** (**Supplementary Material**). Scores were considered as impaired at or above 1.5 standard deviations (SDs) below typical performance (Albert et al., 2011) since there are no cutoff levels for *z*-scores suggested for ADHD (Mostert et al., 2015). To verify real significant change and/or decline over time, we used a statistical procedure called the reliable change index (RCI) (Jacobson and Truax, 1991). Values were considered significant if $\geq$1.96 (**Supplementary Material**).

Assessment of Rating Scales and Test Profile

Case 1

G.F. exhibited normal performance on the MMSE, with a score of 29 (within the cutoff point). The GDS and BAI, administered at all evaluations, did not indicate the presence of symptoms. The IQCODE indicated no changes/decline in cognition.

The clinical evaluation of the two cases can be found in the **Supplementary Material**.

TABLE 1 | Cognitive tests administered and normative data.

Cognitive tests	Domain assessed
Vocabulary and Matrix Reasoning	Estimated intelligence Quotient (IQ)
Digit Span (forward and backward)	Attentional span Working memory
Rey Auditory Verbal Learning Test – RAVLT	Total immediate recall episodic memory (learning), late recall, and recognition of verbal materials
Brief Visual Memory Test – BVMT	Immediate recall episodic memory, late recall, and recognition of visual materials
Boston Naming Test	Naming skills (language)
Trial-Making Test – Parts A and B	Perceptual tracking of a sequence, speed performance, and divided attention, respectively
Stroop Test (scores from third card)	Inhibitory control
Wisconsin Card Sorting Test (WCST) – 64CV	Abstract reasoning ability Ability to shift cognitive strategies
Categorical and phonemic Verbal Fluency	Fluency (executive function) and speed of speech
Continuous Performance Test – CPT II	Sustained attention/alertness, impulsivity, and reaction time

For detail on neuropsychological tests and the sources see Wechsler (1997), Spreen and Strauss, 1998, Lezak et al. (2004), and Strauss et al. (2006).

Test results are presented as *z*-scores (**Table 2**). A graphic representation of the scores and cognition evolution can be found in **Figures 1**, **2**.

The results from the Continuous Performance Test II can be found in **Table 3**.

Case 1 showed normal performance in almost all tests (between -1 and +2.1 *z*-score), except in inhibitory control (–2.3 *z*-score).

This result improved from the first to the second evaluation and improved significantly from the second to the third evaluation, presenting within the expected range at the third evaluation. There were oscillations in performance from one evaluation to the next, but the RCI (**Table 4**) for specific cognitive domains, comparing T3 with T1, revealed an improvement in 6 of the 11 domains; the most consistent finding was a significant improvement in three of the domains {total learning, late recall/visual memory [Brief Visuospatial Memory Test (BVMT)], and inhibitory control (Stroop test—III)}. A decline in performance can be seen in total learning and late recall/verbal memory [Rey Auditory Verbal Learning Test (RAVLT) and Trial Making Test part A (TMT A)], but the differences are not significant. No changes were observed in RAVLT recognition and the Boston Naming Test.

Alertness/sustained attention (CPT-II; **Table 3**) and the number of omission (inattention) and commission (impulsivity) errors were within the normal range in all three evaluations. Changes in the consistency of responses throughout the test [Hit RT (reaction time) Block Change (overall speed of correct answers throughout the test)] and/or lack of improvement in the reaction time over the course of the test [Hit SE (standard error) (measure of response speed consistency) Block Change] showed a predominantly "little slow" reaction time and poor vigilance.

Case 2

T.B. exhibited normal performance on the MMSE, with a score of 27 (above the cutoff point). The BAI and GDS, administered at all evaluations, did not indicate the presence of symptoms. The score on the IQCODE indicated a slight decline.

TABLE 2 | Test's results in *z* score and evaluation times.

Tests	Case 1			Case 2		
	T1	T2	T3	T1	T2	T3
RAVLT – total recall (learning)	1.6	2.1	0.8	0	−0.9	−0.5
RAVLT – late recall	1.8	1.8	1	**−5.8**	**−5.8**	**−5.8**
RAVLT – recognition	1	0.7	1	−0.3	1.1	−0.3
BVMT – total recall (learning)	0.3	1.4	1.2	−2.1	−1.4	−1.1
BVMT – late recall	−0.2	1.2	1.6	**−1.5**	−1.1	−0.3
Boston Naming	1	0.5	1	1.2	1.4	1.6
TMT – A	0.3	1.3	−1	**−3.4**	−1.0	−0.5
TMT – B	0	0.3	0.2	−1.4	−1	−1
Stroop (3)	**−2.3**	**−1.8**	−0.4	**−3.8**	**−2.3**	−0.1
Animal Fluency	−1	−0.8	−0.8	−0.4	−0.4	−0.4
Fluency (FAS)	−0.3	0.1	−0.2	**−1.7**	−0.8	−0.4

Scores in bold are −1.5 z score; T1, Time 1; T2, Time 2; T3, Time 3; (3), Third.

The patient's neuropsychological profile (**Table 2** and **Figure 2**) showed impaired performance in 6 of the 11 domains evaluated, with $z < -3$ in three of them [verbal late recall (RAVLT), attention involving perceptual tracking of a sequence and speed (TMT A), and inhibitory control (Stroop III)]. However, with the exception of her verbal late recall (RAVLT) score, which remained impaired (but stable), and verbal total recall (RAVLT learning), which declined (but not significantly), there was improved performance over time, with scores presenting within the normal range at the third evaluation. The RCI (**Table 4**) showed a significant improvement between T1 and T3 in four domains: visual total recall (learning) and late recall, Boston Naming Test, and inhibitory control (Stroop III). No change was observed in task animal fluency.

The alertness/sustained attention (CPT-II; **Table 3**) score was low, and changes in the consistency of responses were observed throughout the test, indicating that despite a small improvement in reaction time over the course of the test, the patient maintained poor vigilance.

DISCUSSION

Overall, the results of the case assessments showed impairments in cognitive functioning domains mainly related to attention, executive function (inhibitory control and phonemic fluency), and memory, and a predominance of slow reaction times in CPT. Although these cognitive findings do not characterize ADHD by themselves, they are consistent with previous literature (Hervey et al., 2004; Seidman, 2006; Kofler et al., 2013; Faraone et al., 2015; Mostert et al., 2015; Salomone et al., 2016; Weyandt et al., 2017), except for both participants' performance in the working memory domain, which was average. This inconsistency with the literature may reflect possible variations (individual differences) that are found within a larger sample since ADHD in older adults was recently found to be associated with lower cognitive functioning in working memory (Semeijn et al., 2015; Thorell et al., 2017).

We could not verify a possible influence of depressive symptoms on cognitive performance, although there was remission of symptoms in both cases.

The results are also congruent with previous findings regarding the heterogeneity of cognitive expression and intraindividual variations within an evaluation session and across sessions (Salthouse, 2007; Kuntsi and Klein, 2012; Mostert et al., 2015; Thorell et al., 2017). The cognitive profiles of the cases in the present study show differences. The first case 1 exhibited more oscillations from one assessment to another and presented impairment in only one domain (inhibitory control) at T1 and T2 but with an improvement at T3.

The second case exhibited more impaired domains, mainly in the first assessment (T1), with *z*-scores varying between -1.5 and -5.8. At T2, there was an improvement in five of the six scores altered in T1, which leads to questions about a possible subjective factor related to the impact of a lack of familiarity with the evaluation at T1. In contrast to Case 1, Case 2 presented difficulties with memory, notably, verbal late recall (RAVLT), and beyond visual immediate and late recall

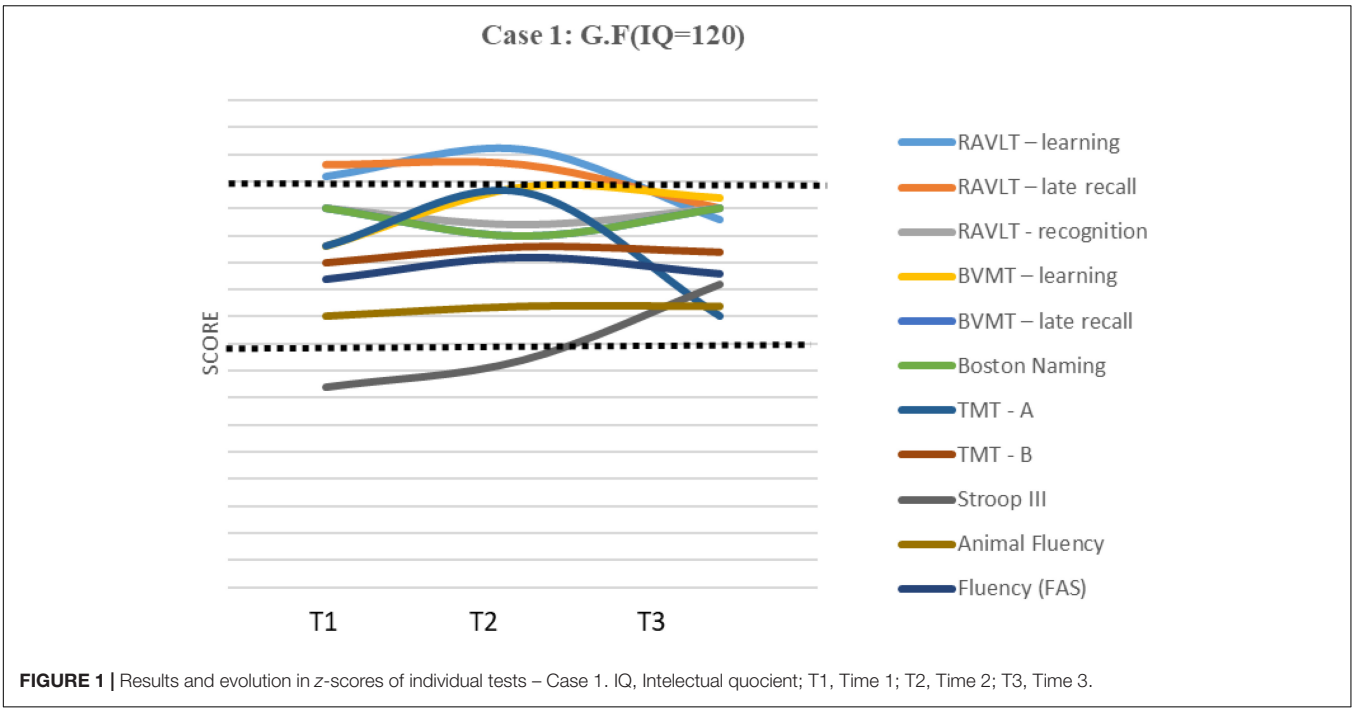

FIGURE 1 | Results and evolution in *z*-scores of individual tests – Case 1. IQ, Intelectual quocient; T1, Time 1; T2, Time 2; T3, Time 3.

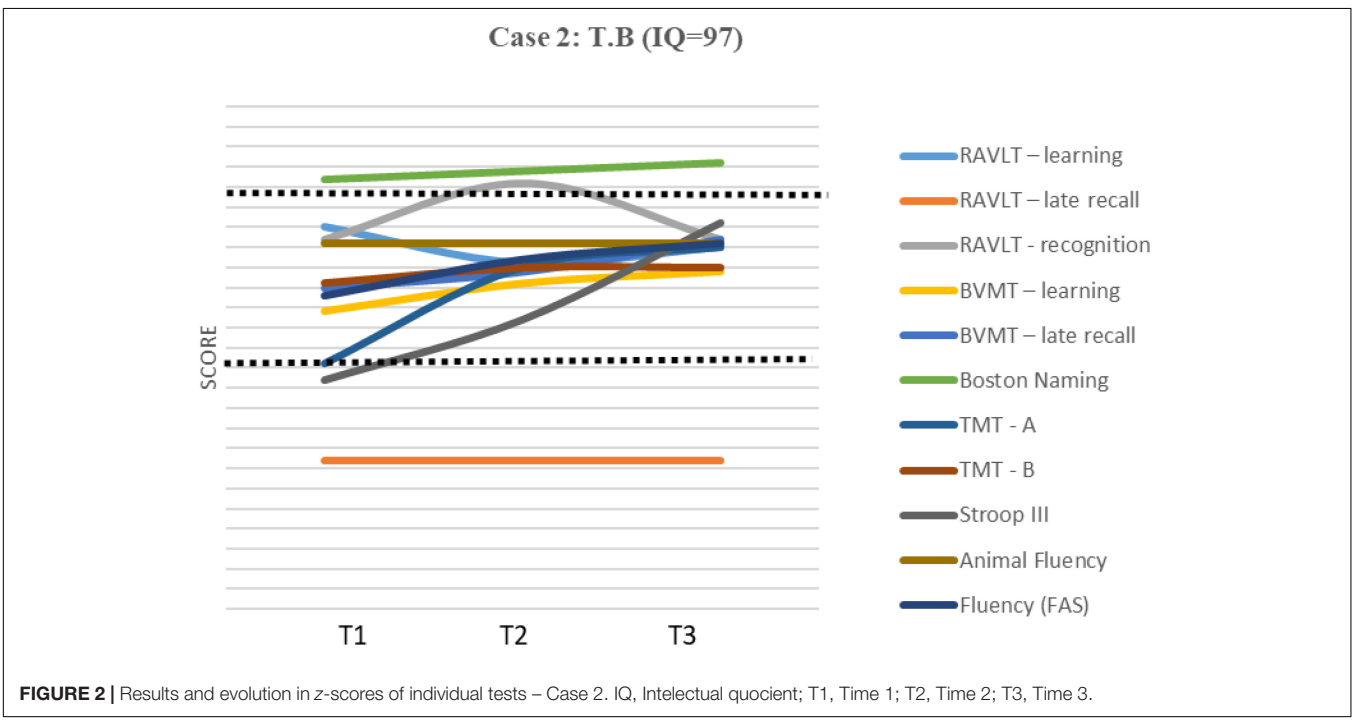

FIGURE 2 | Results and evolution in *z*-scores of individual tests – Case 2. IQ, Intelectual quocient; T1, Time 1; T2, Time 2; T3, Time 3.

(BVMT). However, recognition skills in both tests presented as preserved, suggesting failure in the information search strategy rather than difficulty in storing, as has been found in studies with younger participants with ADHD (Skodzik et al., 2017). In terms of inhibitory control, there was significant improvement on the Stroop (III) test over the course of the evaluations (as was true for Case 1), which suggests practice effects as predicted in previous studies (Goldberg et al., 2015).

Although we do not know how much the patient's cognitive performance impairments were influenced by changes due to aging in the last decade, the impairments are consistent with her lifetime complaints.

Regarding possible cognitive decline, there was no significant decline seen in the comparison between T1 and T3 in both cases. Despite fluctuations in performance, when analyzing individual results (functions that were and were not impaired), there was,

TABLE 3 | Results from Continuous Performance Test – II.

CPT-II	Case 1			Case 2		
	T1	T2	T3	T1	T2	T3
CPT-Omissions (inattention)	A	GP	A	MA	MA	A
CPT-Commissions (impulsivity)	GP	A	A	A	A	GP
CPT – Reaction Time	468.05 LS	447.30 A	499.65 LS	506.45 AS	491.31 LS	490.91 LS
CPT – Vigilance	Poor	A	Poor	A	Poor	Poor

T1, Time 1; T2, Time 2; T3, Time 3. A, Average; GP, good performance; MA, markedly atypical; AS, atypically slow; LS, a little slow.

TABLE 4 | RCI between two times by case and test.

Tests	Case 1						Case2					
	T2–T1		T3–T2		T3–T1		T2–T1		T3–T2		T3–T1	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
RAVLT (total recall)	0.77	0.86	−1.42	−1.64	−1.03	−1.15	−1.23	−1.37	0.49	0.56	−0.61	−0.69
RAVLT (late recall)	0.00	0.00	−0.93	−1.08	−1.18	−1.32	0.00	0.00	0.00	0.00	0.00	0.00
RAVLT (recognition)	−0.46	−0.51	0.36	0.42	0.00	0.00	**2.02**	**2.26**	−1.60	−1.84	0.00	0.00
BVMT (total recall)	1.68	2.53	−0.21	−0.32	1.40	**2.11**	0.97	1.35	0.38	0.61	1.46	**2.02**
BVMT (late recall)	**2.11**	**3.17**	0.52	0.81	**2.81**	**4.23**	0.58	0.81	0.92	1.45	1.75	**2.42**
Boston Naming	−0.88	−1.35	1.15	1.15	0.00	0.00	0.39	0.60	0.51	0.51	0.77	1.19
TMT – A	1.04	1.19	**−2.43**	**−2.77**	−1.39	−1.58	**2.54**	**2.90**	0.46	0.53	**3.00**	**3.42**
TMT – B	0.35	0.38	−0.19	−0.21	0.16	0.17	0.42	0.45	0.00	0.00	0.49	0.53
Stroop III	1.15	1.15	**3.15**	**3.15**	**4.30**	**4.30**	**3.56**	**3.56**	**5.69**	**5.69**	**9.24**	**9.24**
Animal Fluency	0.33	0.33	0.00	0.00	0.33	0.33	0.00	0.00	0.00	0.00	0.00	0.00
Fluency (FAS)	0.60	0.60	−0.32	−0.32	0.24	0.24	1.11	1.11	0.56	0.56	1.67	1.67

RCI in bold, statically significant at a 5% probability level.

in each case, a tendency toward the maintenance of each of their unique cognitive profiles over the three assessments. This tendency provides important clues to the analysis of subsequent changes in the evolution of cognitive functioning.

Due to the fluctuations, a minimum of three consecutive evaluations at baseline may be necessary to acquire a cognitive profile. We hypothesize that longer follow-up of individuals with ADHD is necessary to detect an early real cognitive decline based on objective measures. To minimize the confounding aspect of the fluctuations in clinical practice, the application of RCI may be necessary in addition to controlling for practice effects since improvement due to practice could mask subtle decline in cognition.

For comparison purposes and because a reference more suitable for considering cognitive decline in ADHD is lacking, it is instructive to look at the cutoffs proposed in the DSM-5, which range between 1.0 and 2.0 SDs from the mean for mNCD and >2.0 SDs for dementia. It is expected that some healthy elderly individuals convert to mNCD and some cases of mNCD convert to dementia, both in approximately 4 years, although most mNCD individuals do not develop dementia (Oulhaj et al., 2009; Marcos et al., 2016). Given that ADHD is a little-known condition in the elderly population and that we do not have specific normative data for this population (e.g., pathological limits, floor or ceiling effects), the clinical interpretation of extreme scores in elderly people with ADHD should be examined without precipitation and with thorough consideration of functionality over the lifetime. The development of cognitive tests that are more sensitive and ecological, including functionality scales more appropriate to this specific population, is necessary.

When we investigated the informants' perception of possible cognitive decline using the IQCODE, the informant in Case 2 was asked to consider only the period after the start of the treatment. Despite the objective measures of the assessment, the chronic limitations in the participants' daily functioning, and a slight decline verified through the IQCODE for Case 2, participants were active, worked, and independently performed instrumental and basic activities of daily life during the period in which they were evaluated. More compromised scores and relatively preserved functionality (as in Case 2) could be explained by other possible factors reflecting the individual's achievement in later life to limit the impact of her decline to those few life situations in which she needs to perform at her maximum, relying more with increased age on acquired knowledge and less on solving new problems (Salthouse, 2007).

Another factor that should be considered involves the chronic use of methylphenidate, mainly in Case 2. The treatment may have positive effects on brain structure over time from child to adulthood (Frodl and Skokauskas, 2012) and may improve some cognitive functions such as

working memory, interference control, processing speed, verbal learning (Biederman et al., 2012), sustained attention (Agay et al., 2014), and reaction time (Kofler et al., 2013), although one study failed to find influences on task performance (Mostert et al., 2015). However, the long-term effects of methylphenidate in older adults are not yet known. Thus, it would be interesting for future studies to investigate whether methylphenidate acts on brain structures and plasticity as a neuroprotective factor against cognitive decline, although the basis for such an investigation is speculative.

Our findings do not allow us to make consistent predictions as to whether cognitive deficits become general over time, resulting in greater global cognitive impairment, or if the difficulties in specific domains merely increase in severity over time, with greater impairment in specific situations that are part of the patients' daily functioning. The present study does suggest that, given the complexity and heterogeneity of cognitive expression in ADHD, it will be difficult for future studies to find patterns in the level of oscillations of group performance data to establish a decline in individual cognitive abilities.

In routine clinical assessments, individual characteristics of each participant and multiple other variables unrelated to ADHD, such as the presence of vascular risk factors or pre-existing medical problems, environmental influences, and other factors that might arise over time, should also be taken into consideration. Older adults with ADHD should be subjected to periodic, broad, and thorough clinical evaluations to rule out confounding factors, allowing for appropriate differential diagnoses and enabling the establishment of early and appropriate clinical and/or environmental interventions designed on an individual basis.

CONCLUDING REMARKS

Except for working memory performance, the cognitive profiles found in the two cases are congruent to those reported in other studies conducted in individuals with ADHD. Despite variations from one session to another, it is possible (and necessary) to identify a patient cognitive profile, which should be useful for analysis of cognitive evolution. Consistent cognitive decline was not identified in either of the participants in the 2 years of follow-up. However, these patient profiles represent possible cognitive patterns that may be found in a clinical setting, and they suggest a less pessimistic perspective about cognitive impairments that could be a prodrome of ADHD-related dementia. We also identified some aspects of neuropsychological assessments that may be useful in clinical practice as well as suggestions for individual longitudinal assessments. Further studies should employ longitudinal data, include healthy controls, and avoid the limitations of the present study.

ETHICS STATEMENT

Participants signed a free and informed consent form for the purposes of research participation as well as for the publication of the case report, including all identifiable information/data. The final format of the manuscript along with the authorizations of publication were submitted and approved by the Ethics Committee of the Hospital das Clínicas of the University of São Paulo. Protocol Number 3.118.878.

AUTHOR CONTRIBUTIONS

MK conducted the neuropsychological testing and wrote the present study's results, discussion, and conclusion. MS diagnosed and treated the patients and wrote the case descriptions. APS, GB, and ML contributed to the study design, interpretation, and review of the manuscript. All authors approved the final version of the manuscript for submission and are in accordance with regard to the accuracy and integrity of the work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.01119/full#supplementary-material

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Relationship Between Self-Perceived Health, Vitality, and Posttraumatic Growth in Liver Transplant Recipients

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Our objective was to analyze the differences in posttraumatic growth in 240 liver transplant recipients based on two factors. First, self-perceived health: better (Group 1 = G_1) and worse (Group 2 = G_2). Second, vitality: more (Group 3 = G_3) and less (Group 4 = G_4). The Posttraumatic Growth Inventory, SF-36 Health Survey (Item 2) and SF-12 Health Survey (vitality dimension) were used. Firstly, analyzing main effects recipients with better (G_1) compared to worse (G_2) self-perceived health, showed greater posttraumatic growth. Interaction effects were found on essential posttraumatic growth domains such as new possibilities (p = 0.040), personal strength (p = 0.027), and appreciation of life (p = 0.014). Statistically significant differences showed that among transplant recipients with worse self-perceived health (G_2), those with more vitality had higher levels on abovementioned posttraumatic growth dimensions. However, in transplant recipients with better self-perceived health (G_1) respective dimensions were not significantly influenced by the level of vitality. Among the recipients with less vitality (G_4), those with better self-perceived health showed higher scores on abovementioned posttraumatic growth dimensions. We conclude that positive self-perceived health might compensate for a lack of vitality as well as a high level of vitality may compensate for negative self-perceived health regarding the development of crucial aspects of posttraumatic growth after liver transplantation.

Keywords: liver transplantation, posttraumatic growth, self-perceived health, vitality, patients

INTRODUCTION

At the time of insufficiency or failure of a vital organ, transplantation presents an effective therapeutic alternative offering longer and better quality of life (Kugler et al., 2013). Specifically, liver transplantation is the best option when acute liver disease is triggered with severe short-term prognosis (Karam et al., 2003; Sirivatanauksorn et al., 2012).

Liver transplantation is a critical and determinant moment in life. In general, it gives hope of reestablishing a severely harmed state of health and quality of life, frequently after having lived with

the disease and dysfunctionality for a long time (Zięba et al., 2015). However, transplantation may be a traumatic and highly stressful experience, among other reasons, because of the risks involved. Among these are death, relapse of the disease and dependency on immunosuppressants which may negatively interfere with the recipient's quality of life (Grinyó et al., 2012; Pérez-San-Gregorio et al., 2012). Fantasies about the donor, symptoms of anxiety, depression and posttraumatic stress, or rejection of body image are psychological problems that usually appear after transplantation (Pérez-San-Gregorio et al., 2005; Baranyi et al., 2013; Annema et al., 2015).

The birth of positive psychology in the 1990s motivated development of a salutogenic perspective promoting health by studying, for example, strengths of individuals after a traumatic experience (Wu et al., 2015; Martz and Livneh, 2016). From this perspective, the focus of attention ceases to be placed exclusively on problems derived from transplantation by concentrating on the possibility of developing a positive transformation of life attributed to this traumatic experience (Anand-Kumar et al., 2014). Thus emerged the concept of posttraumatic growth, which alludes to a subjective experience of positive psychological change as a consequence of living through a highly stressful situation (Tedeschi and Calhoun, 2004), which challenges a person's most basic core beliefs, self-concept and setting. It also favors elaboration of new cognitive schemas and development of different coping strategies (Tedeschi and Calhoun, 1995; Martins-da-Silva et al., 2011).

Posttraumatic growth has been widely studied in cancer patients (Casellas-Grau et al., 2018; Sharp et al., 2018; Tobin et al., 2018) and in those who have undergone hematopoietic stem cell transplantation (Forinder and Norberg, 2014; Jeon et al., 2015; Rosenberg et al., 2015). However, there has been relatively few research in liver transplant recipients. On the one hand, respective studies indicate that posttraumatic growth increases identification of recipients with their family and with other recipients (Scrignaro et al., 2016). On the other hand, they point to a close association between development of strong posttraumatic growth and the use of an affective, predominantly positive tone in telling about past life events (Zięba et al., 2015). Pérez-San-Gregorio et al. (2017b) also showed that a high level of posttraumatic growth is related to more use of adaptive, healthy coping strategies.

Other studies on posttraumatic growth and quality of life did not find a significant positive relationship between these two factors, such as the one by Moore et al. (2011) with a sample of 202 patients diagnosed with hepatobiliary carcinoma. A similar conclusion was found in a study by Fox et al. (2014) with 64 lung transplant recipients, which found only a minimal association between posttraumatic growth and quality of life related to physical functioning.

However, to date it is still unclear which mechanisms underlie the development of posttraumatic growth (Tedeschi and Calhoun, 2004). Nevertheless, it is clear that it involves cognitive and affective-motivational processes to be able to restructure cognitive schemata and their emotional underpinnings. In the context of posttraumatic growth after liver transplantation the construct of self-perceived health is very relevant. There is growing evidence for its importance regarding quality of life across a wide spectrum of disease entities. Thus, its influence on quality of life has been demonstrated in patients with cancer (Cameron et al., 2012; Hirsch et al., 2012), cardiovascular pathology (Bachmann et al., 2016; Ko and Boo, 2016), hepatitis and HIV (Marcellin et al., 2011; Elliott et al., 2017; Zhu et al., 2017). A study by Martín-Rodríguez et al. (2012) demonstrated the influence of self-perceived health on mental health in cirrhosis patients on the transplant waiting list and liver transplant recipients. According to a study by Pérez-San-Gregorio et al. (2013) on 168 liver transplant recipients, those with worse self-perceived health showed worse quality of life than those with better self-perceived health, especially in the bodily pain and general health dimensions. Against this backdrop, self-perceived health can be seen as a construct which can assist in predicting a patient's affective development and potential posttraumatic growth after liver transplantation.

A second construct closely linked to posttraumatic growth is vitality (Tedeschi and Calhoun, 1996, 2004). A "positive feeling of having energy available to the self" (Nix et al., 1999, p. 266) is a widely accepted definition, accentuating the aspect of subjectively assessing one's own emotional state. Even though self-perceived health and vitality are regarded as closely associated as, for example, in the construction of the SF-36, there is some evidence (Guérin, 2012) that it makes sense to disentangle them, as self-perceived health embraces the cognitive component of health-related self-assessment, whereas (self-perceived) vitality its affective-motivational component.

Against this backdrop, our study analyzes the differences in posttraumatic growth after liver transplantation as a function of two factors, self-perceived health and vitality. We specifically hypothesized that better self-perceived health and higher vitality of transplant recipients may mutually facilitate higher posttraumatic growth.

MATERIALS AND METHODS

Participants

This research was approved by the Ethics Committee of the Virgen del Rocío University Hospital of Seville. At the beginning of recruitment all 569 patients still alive from a total clinical sample of 1053 recipients who had undergone transplantation surgery at the Virgen del Rocío University Hospital in Seville from 1990 to 2014 were informed about the possibility of study participation by the Association of Liver Transplant Recipients and the Hepatic-Biliary-Pancreatic Surgery and Liver Transplant Unit. Inclusion criteria for participants were as follows: (a) over 18 years of age, (b) informed consent, (c) reception of only one liver transplant. Exclusion criteria were (a) difficulties in understanding the evaluation instruments, (b) severe or disabling psychiatric disorder. The recruited sample consisted of 240 patients, 185 men and 55 women, with a mean age of 60.21 (SD = 9.30) years. Of the recipients, 61.7, 22.5, and 15.8% had a low (did not complete high school), intermediate (high school education), and higher formal education (A level), respectively. For further details, see Pérez-San-Gregorio et al. (2017a).

Instruments

Each participant filled out the 21 items on the *Posttraumatic Growth Inventory* (Tedeschi and Calhoun, 1996) which evaluates perception of personal benefits after experiencing a traumatic event. This instrument is structured in a Likert-type scale from 0 ("I did not experience this change as a result of my crisis") to 5 ("I experienced this change to a very great degree as a result of my crisis") in the positive direction.

The scale includes five domains of posttraumatic growth named new possibilities, relating to others, personal strength, spiritual change, and appreciation of life. In the Spanish version of this instrument (Weiss and Berger, 2006), we found the following Cronbach's alphas in our sample of patients: 0.94 for personal strength, 0.88 in relating to others, 0.80 in new possibilities, 0.77 in personal strength, 0.76 in appreciation of life and 0.73 in spiritual change.

To form the various levels of independent variables, the participants answered Item 2 on the Spanish version of the *SF-36 Health Survey* (Alonso et al., 1995) and the vitality subscale of the *12-Item Short-Form Health Survey (SF-12v.2)* (Ware et al., 2002; Maruish, 2012).

Procedure

A 2 × 2 factorial design was carried out with the independent variables self-perceived health and vitality.

(a) *Self-perceived health*, with two levels (*better* or *worse*). This variable was selected based on the scores on Item 2 of the SF-36 ("Compared to 1 year ago, how would you rate your health in general now?"): (1) G_1: liver transplant recipients with *better* self-perceived health: patients with scores over 54.2%, which referred to the following answers: "somewhat better now than 1 year ago" and "much better now than 1 year ago," forming a subgroup of 110 patients, and (2) G_2: liver transplant recipients with *worse* self-perceived health: patients with scores equal to or less than 54.2%, which referred to the following answers: "about the same than 1 year ago," "somewhat worse now than 1 year ago" and "much worse now than 1 year ago," forming a subgroup of 130 patients.

(b) *Vitality*, with two levels (*more* and *less*). This variable was selected based on the scores on the SF-12 vitality dimension ("How much of the time during the past 4 weeks, did you have a lot of energy?"): (1) G_3: liver transplant recipients with *more* vitality: patients with scores over 45.4%, which referred the following answers: "most of the time" and "all of the time," forming a subgroup of 131 patients, and (2) G_4: liver transplant recipients with *less* vitality: patients with scores equal to or less than 45.4%, which referred to the following answers: "some of the time," "a little of the time" and "none of the time," forming a subgroup of 109 patients.

To establish the two subgroups corresponding to the factors self-perceived health and vitality, we proceeded as follows: First, the scores of each patient were taken into account for both variables, which varied from 0 to 100. Second, for both variables the scores were ordered from least to most. Afterward the accumulated percentages of the frequency distribution were taken into account two form two subgroups of patients for each variable, which embraced approximately half of the sample. From a clinical perspective, these divisions into two subgroups in each of the factors are very relevant, since they allow the categorization of patients with similar characteristics.

Statistical Analysis

Pearson's chi-squared was used to compare the categorical variables (gender, marital status, education, and employment), and for the quantitative variables (age and months since transplantation), the *t*-test for independent samples was applied.

We also applied a covariance analysis to analyze the influence of two independent factors on the level of posttraumatic growth: level of self-perceived health (better or worse) and vitality (more or less). In this analysis, first age of the transplant patient was included as a covariate. In a second analysis age and time since transplantation were included as covariates. Results with $p < 0.05$ were regarded as significant, results with $p < 0.10 \geq 0.05$ as statistical trend. Effect sizes were calculated using Cohen's w (for categorical variables) and Cohen's *d* (for quantitative variables). The data were analyzed with the SPSS 22 statistical program.

RESULTS

The group of liver transplant recipients with better self-perceived health (G_1) was made up of 89 men and 21 women with a mean age of 59.38 years (SD = 7.68), while the one with worse self-perceived health (G_2) was made up of 96 men and 34 women, with a mean age of 60.91 (SD = 10.46). The group of liver transplant recipients with more vitality (G_3) was made up of 105 men and 26 women with a mean age of 60.12 (SD = 8.79), and the one with less vitality (G_4) had 80 men and 29 women with a mean age of 60.31 (SD = 9.92). The sociodemographic and clinical data for the four groups of liver transplant recipients are summarized in **Tables 1**, **2**.

With regard to the analysis of socio-demographic variables in better versus worse self-perceived health, there was a statistical trend in the direction of worse self-perceived health in recipients with a partnership (small effect size). Regarding the comparison of more versus less vitality there was a significant difference showing less vitality in recipients having a lower level of education with a small effect size. Furthermore, those recipients not working showed a statistical trend toward less vitality (small effect).

Regarding clinical variables those recipients with longer time since transplantation showed significantly poorer self-perceived health with a large effect size ($p < 0.001$, $d = -0.947$; **Table 1**).

In the next step of analysis we were interested in differences in posttraumatic growth in above mentioned subgroups controlling for age (**Table 3**). Regarding the level of posttraumatic growth, interaction effects were found between self-perceived health and vitality factors in the following variables: new possibilities [$F_{(1,233)} = 4.278$, $p = 0.040$], personal strength [$F_{(1,233)} = 4.951$, $p = 0.027$], and appreciation of life [$F_{(1,233)} = 6.109$, $p = 0.014$] (**Table 3**). Regarding simple effects, as shown in **Figure 1** and in **Tables 4**, **5**, we found that among transplant recipients with worse self-perceived health, those with more vitality scored

TABLE 1 | Comparison of sociodemographic and clinical variables between two groups with better (G_1) and worse (G_2) self-perceived health.

	Level of self-perceived health		Intergroup comparisons	Effect sizes
	Better (G_1) n = 110	Worse (G_2) n = 130		
	M (*SD*)	*M* (*SD*)	*t* (*p*)	Cohen's *d*
Age	59.38 (7.68)	60.91 (10.46)	$t_{(1,233.52)}$ = 1.300 (0.195)	−0.166 N
Months since transplantation	57.17 (54.83)	113.66 (64.05)	$t_{(1,237.96)}$ = 7.361 (<0.001)	−0.947 L
	%	%	χ^2 (*p*)	Cohen's *w*
Gender			1.683 (0.195)	−0.084 N
Male	80.9	73.8		
Female	19.1	26.2		
Marital status			3.776 (0.052)	−0.125 S
With partner	73.6	83.8		
Without partner	26.4	16.2		
Education			2.573 (0.276)	0.104 S
Low	63.6	60		
Medium	24.5	20.8		
High	11.9	19.2		
Employment			1.689 (0.194)	0.084 N
Working	5.5	10		
Not working	94.5	90		

N, null effect size; S, small effect size; L, large effect size.

TABLE 2 | Comparison of sociodemographic and clinical variables between two groups with more (G_3) and less (G_4) vitality.

	Level of vitality		Intergroup comparisons	Effect sizes
	More (G_3) n = 131	Less (G_4) n = 109		
	M (*SD*)	*M* (*SD*)	*t* (*p*)	Cohen's *d*
Age	60.12 (8.79)	60.31 (9.92)	$t_{(1,217.91)}$ = 0.155 (0.877)	−0.020 N
Months since transplantation	86.47 (64.20)	89.33 (68.77)	$t_{(1,238)}$ = 0.332 (0.740)	−0.042 N
	%	%	χ^2 (*p*)	Cohen's *w*
Gender			1.538 (0.215)	−0.08 N
Male	80.2	73.4		
Female	19.8	26.6		
Marital status			0.009 (0.926)	0.006 N
With partner	79.4	78.9		
Without partner	20.6	21.1		
Education			6.737 (0.034)	0.168 S
Low	55	69.7		
Medium	24.4	20.2		
High	20.6	10.1		
Employment			3.037 (0.081)	−0.112 S
Working	10.7	4.6		
Not working	89.3	95.4		

N, null effect size; S, small effect size.

higher on the domains new possibilities (p = 0.017, d = 0.427), personal strength (p = 0.003, d = 0.541), and new appreciation of life (p = 0.053, d = 0.346) the latter by a statistical trend, while those with better self-perceived health showed no differences in those variables (**Table 4** and **Figure 1**). We also found that among transplant recipients with less vitality, those with better self-perceived health showed higher scores (more posttraumatic growth) than those with worse self-perceived health on the scales new possibilities (p = 0.005, d = 0.598), personal strength (p = 0.003, d = 0.627), and new appreciation of life (p = 0.001, d = 0.718) variables, while those with more vitality did not show these differences as a function of self-perceived health (**Table 5** and **Figure 1**).

Concerning the main effects, we found statistically significant differences among transplant recipients with better and worse self-perceived health in the new possibilities (p = 0.023; d = 0.298), personal strength (p = 0.020; d = 0.303), and appreciation of life (p = 0.006; d = 0.363) variables, and total posttraumatic growth score (p = 0.031; d = 0.281). Specifically, those transplant recipients with better self-perceived health showed more posttraumatic growth (**Table 3**).

In a further analysis we looked at the difference in posttraumatic growth controlling for age and time since transplantation (**Table 6**). A statistically significant interaction effect was found for appreciation of life [$F_{(1,233)}$ = 4.799, p = 0.029]; the subscales new possibilities [$F_{(1,233)}$ = 2.842, p = 0.093]; and personal strength [$F_{(1,233)}$ = 3.227, p = 0.074] showed a statistical trend. Regarding simple effects (**Tables 7**, **8**) we also found that among transplant recipients with less vitality, those with better self-perceived health showed higher scores (more posttraumatic growth) than those with worse self-perceived health on the scale new appreciation of life ($p < 0.001$, d = 0.813) as shown in **Table 8** and **Figure 2**.

DISCUSSION

The current study analyses the mutual associations of self-perceived health and vitality on posttraumatic growth in liver transplant recipients. We divided the sample according to better or worse self-perceived health and more or less vitality into four groups. With regard to socio-demographic characteristics in recipients with more versus less vitality there was a statistically significant difference with regard to education. Lower education was associated with a lower level of vitality by a small effect size. Furthermore there was a statistical trend with a small effect size indicating that recipients not working reported less vitality. Comparing recipients with better versus worse self-perceived health those patients having a partnership showed a statistical trend with a small effect size in the direction of worse self-perceived health. As one might have expected in those recipients with worse self-perceived health a significantly longer time-span had passed since transplantation. Particularly long term treatment by immunosuppressants and the associated side effects

TABLE 3 | Posttraumatic growth in liver transplant recipients based on level of self-perceived health and level of vitality with age as covariate.

	Level of self-perceived health *M* (*SD*)[1]		Level of vitality *M* (*SD*)[1]		Main effects		Interaction effects
	Better *n* = 110	Worse *n* = 130	More *n* = 131	Less *n* = 109	Self-perceived health $F_{(1,233)}$ *p* (d^2)	Vitality $F_{(1,233)}$ *p* (d^2)	$F_{(1,233)}$ *p*
Relating to others	3.41 (1.30)	3.19 (1.20)	3.38 (1.21)	3.22 (1.29)	1.737	1.026	1.409
					0.189 (0.175 N)	0.312 (0.127 N)	0.236
New possibilities	3.20 (1.32)	2.82 (1.22)	3.10 (1.22)	2.93 (1.30)	5.271	1.103	4.278
					0.023 (0.298 S)	0.295 (0.134 N)	0.040
Personal strength	3.47 (1.33)	3.08 (1.24)	3.42 (1.23)	3.13 (1.32)	5.496	2.958	4.951
					0.020 (0.303 S)	0.087 (0.227 S)	0.027
Appreciation of life	4.05 (1.31)	3.59 (1.22)	3.83 (1.22)	3.82 (1.30)	7.695	0.002	6.109
					0.006 (0.363 S)	0.962 (0.007 N)	0.014
Spiritual change	2.30 (1.79)	2.18 (1.66)	2.29 (1.67)	2.20 (1.78)	0.281	0.150	0.327
					0.597 (0.069 N)	0.699 (0.052 N)	0.568
Total score PTGI	70.68 (24.45)	64.03 (22.70)	69.05 (22.69)	65.67 (24.33)	4.691	1.217	3.794
					0.031 (0.281 S)	0.271 (0.143 N)	0.053

[1]*Means (standard deviation): higher scores show more posttraumatic growth. Recipients' age has been introduced as covariate in the analysis.* [2]*Cohen's d index: N, null effect size; S, small effect size.*

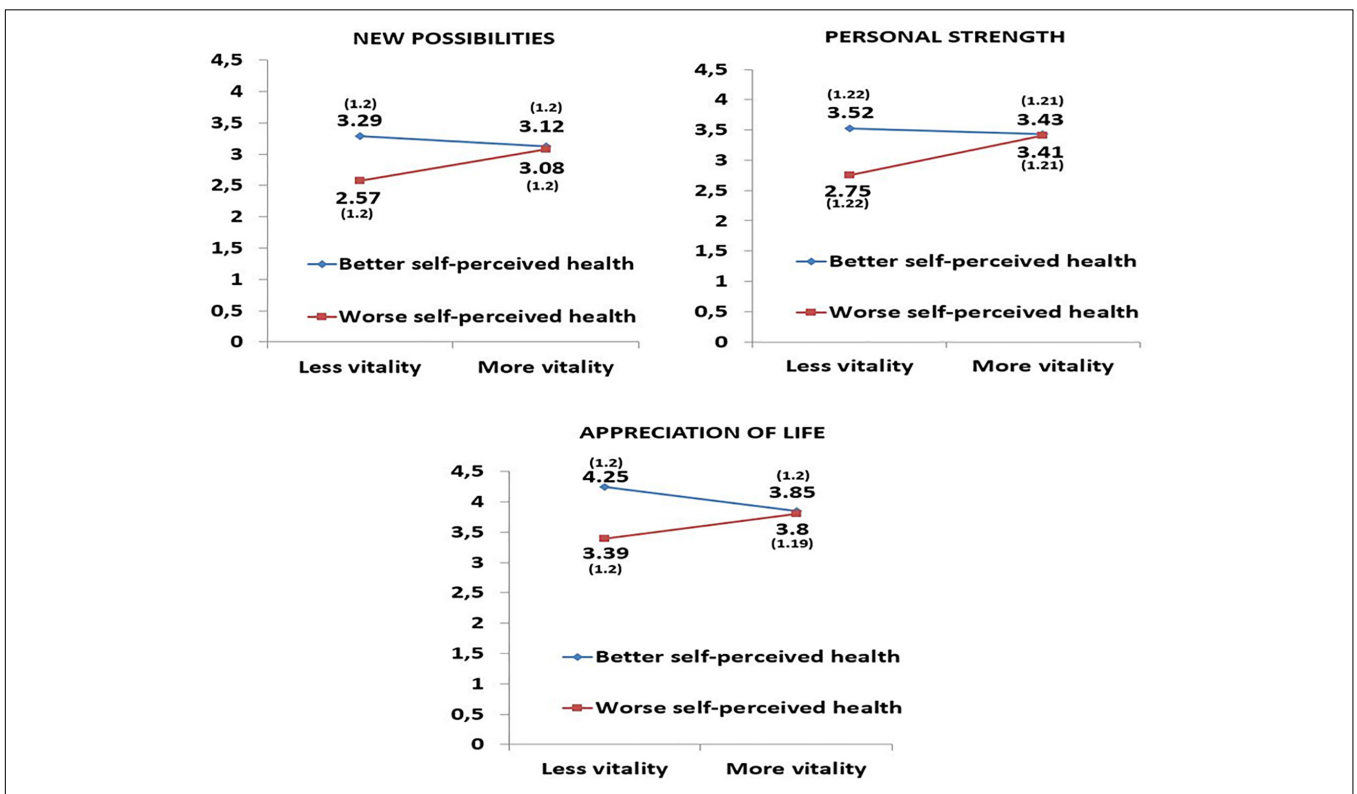

FIGURE 1 | Interaction effects between the two factors self-perceived health (better and worse) and vitality (more and less). Means (standard deviations) adjusted for age of liver transplant recipients.

might have been one important cause for an increase in health problems which corresponds to a decline in self-perceived health (Kugler et al., 2009).

Regarding the influence of self-perceived health and vitality on posttraumatic growth controlling for age significant interaction effects were found on the posttraumatic growth dimensions new possibilities, personal strength and new appreciation of life as opposed to the dimensions relating to others and spiritual change. Further analysis revealed that participants with worse self-perceived health scored significantly higher on

TABLE 4 | Simple effects: comparisons between liver transplant recipients with better (G_1) and worse (G_2) self-perceived health at each of the levels of vitality.

Level of vitality	Better self-perceived health (G_1) n = 110		Worse self-perceived health (G_2) n = 130	
	p	Cohen's d	p	Cohen's d
		New possibilities		
More-less	0.502	−0.139 N	0.017	0.427 S
		Personal strength		
More-less	0.737	−0.070 N	0.003	0.541 M
		New appreciation of life		
More-less	0.112	−0.332 S	0.053	0.346 S

N, null effect size; S, small effect size; M, medium effect size.

TABLE 5 | Simple effects: comparisons between liver transplant recipients with more (G_3) and less (G_4) vitality at each level of self-perceived health.

Level of self-perceived health	More vitality (G_3) n = 131		Less vitality (G_4) n = 109	
	p	Cohen's d	p	Cohen's d
		New possibilities		
Better-worse	0.859	0.003 N	0.005	0.598 M
		Personal strength		
Better-worse	0.925	0.016 N	0.003	0.627 M
		New appreciation of life		
Better-worse	0.813	0.042 N	0.001	0.718 M

N, null effect size; M, medium effect size.

abovementioned posttraumatic growth domains when they felt more vitality. On the other hand, in recipients with less vitality, the scores on these dimensions were higher when they had better self-perceived health. When we introduced time since transplantation as covariate in our analysis we found a significant interaction effect on the dimension appreciation of life and the dimensions personal strength and new possibilities showed a statistical trend. Analysis of the simple effects on the dimension appreciation of life revealed similar to the previous analysis that recipients with less vitality scored higher with better self-perceived health.

Previous studies confirm the positive association between self-perceived health and posttraumatic growth. In the article by Fox et al. (2014), lung transplant recipients who experienced more posttraumatic growth showed a better self-perceived general health. Similarly, a meta-analysis of 38 studies of persons diagnosed with cancer or HIV showed evidence that posttraumatic growth was related to better self-perceived physical and mental health (Sawyer et al., 2010). The construct of self-perceived health can be seen as the cognitive component of health-related self-assessment, whereas self-perceived vitality embraces its affective-motivational component. Vitality is characterized by three dimensions (Van Steenbergen et al., 2016): energy, or feeling energized; motivation, that means putting effort in achieving goals; and resilience, which consists of the ability to deal with everyday problems and challenges in life. Thus as our first analysis controlling for age showed having more vitality strengthened posttraumatic growth in those participants who did not realize a satisfactory state of health. Similarly, among the recipients who felt insufficient energy and motivation the awareness of better self-perceived health facilitated the awareness of personal strength, new possibilities and appreciation of life. In this context the close link between cognitive and affective-motivational aspects of mental well-being becomes apparent. Despite a lack of positive thinking the recipient, who feels energized, may realize new opportunities. On the other hand, a

TABLE 6 | Posttraumatic growth in liver transplant recipients based on level of self-perceived health and level of vitality with age and time since transplantation as covariates.

	Level of self-perceived health M (SD)[1]		Level of vitality M (SD)[1]		Main effects		Interaction effects
	Better n = 110	Worse n = 130	More n = 131	Less n = 109	Self-perceived health $F_{(1,233)}$ p (d^2)	Vitality $F_{(1,233)}$ p (d^2)	$F_{(1,233)}$ p
Relating to others	3.53 (1.34)	3.09 (1.26)	3.37 (1.19)	3.25 (1.27)	6.223	0.539	0.606
					0.013 (0.338 S)	0.464 (0.097 N)	0.437
New possibilities	3.32 (1.35)	2.72 (1.27)	3.08 (1.20)	2.96 (1.29)	11.036	0.617	2.842
					0.001 (0.458 S)	0.433 (0.096 N)	0.093
Personal strength	3.60 (1.37)	2.96 (1.28)	3.40 (1.21)	3.16 (1.30)	12.672	2.047	3.227
					<0.001 (0.483 S)	0.154 (0.191 N)	0.074
Appreciation of life	4.13 (1.18)	3.52 (1.49)	3.82 (1.21)	3.84 (1.30)	11.344	0.020	4.799
					0.001 (0.454 S)	0.886 (−0.016 N)	0.029
Spiritual change	2.44 (1.86)	2.06 (1.74)	2.27 (1.65)	2.23 (1.77)	2.331	0.023	0.054
					0.128 (0.211 S)	0.880 (0.023 N)	0.817
Total score PTGI	73.05 (25.08)	61.76 (23.54)	68.61 (22.27)	66.20 (23.88)	11.606	0.643	2.289
					0.001 (0.464 S)	0.424 (0.104 N)	0.132

[1]*Means (standard deviation): higher scores show more posttraumatic growth. Recipients' age and time elapsed since transplantation have been introduced as covariates in the analysis.* [2]*Cohen's d index: N, null effect size; S, small effect size.*

TABLE 7 | Simple effects on appreciation of life: comparisons between liver transplant recipients with better (G_1) and worse (G_2) self-perceived health at each of the levels of vitality.

Level of vitality	Better self-perceived health (G_1) n = 110		Worse self-perceived health (G_2) n = 130	
	p	Cohen's d	p	Cohen's d
More-less	0.123	−0.318 S	0.118	0.276 S

S, small effect size.

TABLE 8 | Simple effects on appreciation of life: comparisons between liver transplant recipients with more (G_3) and less (G_4) vitality at each level of self-perceived health.

Level of self-perceived health	More vitality (G_3) n = 131		Less vitality (G_4) n = 109	
	p	Cohen's d	p	Cohen's d
Better-worse	0.293	−0.199 N	<0.001	0.813 L

N, null effect size; L, large effect size.

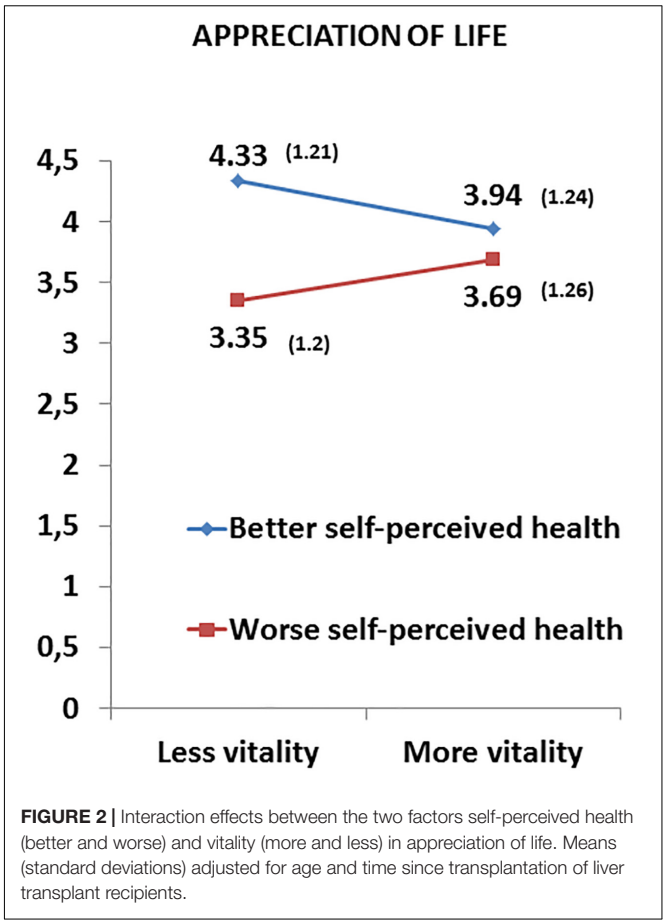

FIGURE 2 | Interaction effects between the two factors self-perceived health (better and worse) and vitality (more and less) in appreciation of life. Means (standard deviations) adjusted for age and time since transplantation of liver transplant recipients.

lack of energy might be compensated for by positive thoughts of one's state of health. Respective associations were weaker when controlling for time since transplantation, nevertheless this analysis also revealed a large effect of better self-perceived health on the posttraumatic growth dimension appreciation of life in recipients with less vitality.

This is in line with the theory of posttraumatic growth by Tedeschi and Calhoun (1996, 2004) in which post-traumatic stress is understood to be the engine of post-traumatic growth and cognitive and affective processes are closely intertwined. The degree of posttraumatic growth reported tends to be related to the extent of cognitive engagement or rumination about elements related to the stressful event. The cognitive engagement corresponds to the level of threat associated with the traumatic event. Greater growth has been reported for individuals who reported higher levels of stress or threat (Linley and Joseph, 2004; Weiss, 2004). However, to date it is still not clear why some individuals can grow after a critical event and others are simply overwhelmed by the situation (Tedeschi and Calhoun, 2004). Specific cognitive and affective resources are underlying the ability to grow and according to our findings self-perceived health as well as vitality may be seen as relevant factors in this highly complex process.

In summary, our study could confirm differences in posttraumatic growth of liver transplant recipients according to their self-perceived health and vitality. These results demonstrate potential possibilities for strengthening posttraumatic growth (Jeon et al., 2015). Just as group psychotherapy and cognitive behavioral therapy are performed in cirrhosis patients on the transplantation waiting list (Su et al., 2014; Ramírez et al., 2015), it would be beneficial to implement interventions of this type in the post-transplant stage for the purpose of improving self-perceived health and vitality with potentially beneficial consequences for posttraumatic growth and quality of life. Integrating psychological diagnostics, therapy and outcome evaluation (Geiser et al., 2001) in the protocols for long-term follow-up of liver transplant recipients would facilitate the identification and reduction of psychological risk factors, thereby increasing the likelihood of optimizing recipients' outcome (Morana, 2009; Dąbrowska-Bender et al., 2018).

Finally, it would be advisable, with a view to future lines of research, to consider some limitations observed in the design of this study. For example, the etiology of the liver disease leading to transplantation was not taken into consideration. There might have been differences in posttraumatic growth between transplantation recipients with alcoholic, viral or metabolic liver cirrhosis. Furthermore, due to its cross-sectional design, it was not possible to analyze the long-term development of specific alterations. A longitudinal study would solve this problem, and could reveal causal relationships between self-perceived health, vitality and posttraumatic growth. Furthermore, there are other variables which could affect the relationship between the above mentioned variables such as personality traits, which were not taken into account.

For future studies a methodological approach based on the narrative theory as suggested by Gangeri et al. (2018) might be interesting to shed light on the complex mechanisms of posttraumatic growth. Thus, instead of quantifying different parameters by questionnaires, it would be important to analyze

the personal narrative of recipients about life changes after liver transplantation.

ETHICS STATEMENT

Ethics Committee of the Virgen del Rocío University Hospital of Seville. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the work, revised the manuscript critically for important intellectual content, and approved the final version of the manuscript to be submitted. JF-S, AM-R, RC, and MÁP-S-G performed the bibliography research about the topic, collected, analyzed, and interpreted the data, and drafted the manuscript. MB-M, MLA-N, MÁG-B, and MR-G conceived and designed the work, and analyzed and interpreted the data.

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As Time Goes by: Anxiety Negatively Affects the Perceived Quality of Life in Patients With Type 2 Diabetes of Long Duration

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Introduction: Age-related medical conditions are increasing worldwide. Type 2 Diabetes mellitus (T2DM) represents a chronic disease, which affects a large amount of general population, accounting for over 90% of diabetes mellitus (DM) cases.

Purpose: As psychopathological symptoms frequently occur in medical conditions, our study aimed at exploring whether psychological factors and metabolic control may affect health related quality of life (HRQoL).

Methods: Forty five patients with T2DM were consecutively recruited and assessed with a psychodiagnostic battery: Hamilton Anxiety Rating Scale (HAM-A), Beck Depression Inventory II edition (BDI-II) and the 36-Item Short Form Health Survey (SF-36), including indexes Physical and Mental Component Summary (PCS, MCS). Moreover, time since DM diagnosis and glycated hemoglobin (HbA1c) values were detected.

Results: Participants (mean age 65.3 ± 5.9 years) had a mean time since diagnosis of 11.6 ± 6.7 years, and showed a good metabolic control as highlighted by mean HbA1c values 7.1 ± 0.9%. Median HAM-A score [25(20.7–30.6)], represented high prevalence of anxious symptoms. A moderate expression of depressive symptoms was observed [BDI-II score: 13(8.3–21.4)]. A multiple regression analysis, after correcting for age, BMI, HbA1c value and BDI-II score, showed the perceived quality of life relative to PCS was significantly related to both disease duration ($\beta = -0.55$, $p = 0.03$, $SE = 0.25$) and HAM-A scores ($\beta = -0.52$, $p = 0.04$, $SE = 0.24$). Moreover, both HAM-A ($\beta = -0.67$, $p = 0.01$, $SE = 0.26$) and BDI-II ($\beta = -0.48$, $p = 0.02$, $SE = 0.20$) scores were independently predictive of MCS. Metabolic control, instead, was not a significant predictor.

Conclusion: Our study suggests a predictive role of both anxiety levels and time since diagnosis in perceived HRQoL in T2DM patients. PCS was associated with anxiety and time since diagnosis and MCS was associated with anxiety and depressive symptoms but not with diabetes duration or metabolic control. These data could be useful to plan T2DM training programs focused on psychological health concerns, possibly leading to a healthy self-management and a better perceived HRQoL, even assisting patients in reducing the negative effect due to the chronicization of T2DM.

Keywords: chronic diseases, anxiety, depression, quality of life, physical component summary, mental component summary, type 2 diabetes

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INTRODUCTION

Chronical diseases and related outcomes may lead to psychological consequences as they impact both on psychological health and quality of life (Martino et al., 2018a; Kelly et al., 2019). It is known that almost apart from the etiopathological mechanisms, dissimilar age-related chronic diseases may elicit similar psychopathological features, which can even predict morbidity and mortality independently of a comprehensive variety of potential confounders (Kiecolt-Glaser et al., 2002; Lapolla et al., 2012; Martino et al., 2018b; Kelly et al., 2019). Several studies have been conducted exploring both depression and anxiety as predictors of chronic diseases and related outcomes (Atteritano et al., 2013; Catalano et al., 2018). Psychological aspects may also effort people behavior, influencing the management of chronic diseases (Castelnuovo et al., 2015; Van Houtum et al., 2015; Stanton and Hoyt, 2017; Quattropani et al., 2019; Settineri et al., 2019; Vicario et al., 2019). One of the most demanding disease to manage with, due to several variety related concerns, is represented by diabetes mellitus (DM). Differently from autoimmune type 1 DM, Type 2 Diabetes Mellitus (T2DM), also known as adult diabetes, accounts for over 90% of cases and is characterized by a high level of blood glucose due to the body failure to correctly metabolize glucose for the body's needs, in a context of insulin resistance and relative insulin deficiency. T2DM is a pandemic metabolic disease, with significant morbidity and mortality, estimated to affect at least 285 million people worldwide, and this number will rise to 438 million by the year 2030 (Whiting et al., 2011). It is known that specific features as compliance and adherence are fundamental to adequately manage T2DM long life, reducing the wide related outcomes (Markle-Reid et al., 2018). Accordingly, the emotional distress related to the chronic affection, needs a psychological adaptation process to integrate illness experience into individual's life context (Whittemore and Dixon, 2008; Whittemore et al., 2010; Van Houtum et al., 2015; Vari et al., 2017; Marchini et al., 2018). Thus, individuals with T2DM try to manage with the stress of living with such chronic illness (Whittemore et al., 2010; Savarese et al., 2018), developing psychological adaptation and adherence through the acceptance of T2DM, including toleration, approval, integration and identification (Lo Coco et al., 2005; Schmitt et al., 2014, 2018; Ebrahimi et al., 2016; Stanton and Hoyt, 2017; Lai et al., 2019). It has been demonstrated that a low psychological adjustment to DM is linked to a worse metabolic control and self-management and lower perceived quality of life (HRQoL) (Misra and Lager, 2008; Smith et al., 2013). Jing et al. (2018) showed that several factors as physical exercise, glucose check, outcomes, time since diagnosis and depression were significantly associated with HRQoL. Individuals with T2DM often report higher levels of depressive symptoms, due to both related complications and disease-management, leading to required life-style changes (Das-Munshi et al., 2007; Bouwman et al., 2010; Van Houtum et al., 2015; Sartorius, 2018). Moreover, external factors as employment and marital status, body mass index (BMI), body image, smoking habits and physical activity could predict depression in T2DM (Bouwman et al., 2010; Guicciardi et al., 2014, 2015; Rosa et al., 2019). Mainly Bouwman et al. (2010) highlighted the association between the higher prevalence of depressive but not anxious symptoms and diabetes. Smith et al. (2013) in a systematic review and meta-analysis found a significant and positive association between diabetes and both anxiety symptoms and anxiety disorder. Anderson et al. (2002) in a meta-analytic review highlighted anxiety disorders are associated with hyperglycemia in T2DM patients. Shinkov et al. (2018) reported the increased prevalence of depression and anxiety among subject with T2DM and metabolic syndrome, underlining depression and anxiety were positively related with age and female gender. Amiri and Behnezhad (2019) confirmed data on the association between anxiety and diabetes, concluding that its outcomes remain controversial and suggesting that diabetes is an important risk factor for anxiety symptoms and therefore that healthy status can prevent anxiety. Nevertheless, the debate about the association between psychopathological factors and chronic medical conditions is still open and there is an increasing interest on the specific role psychological determinant may have on chronic diseases and healthy related quality of life (HRQoL) (Trikkalinou et al., 2017). On the basis of previous studies which explored HRQoL in patients with T2DM (Hasan et al., 2016; Markle-Reid et al., 2018; Nguyen et al., 2018), the aim of our research was to further investigate the relationship between anxious and depressive symptoms, time since T2DM diagnosis and metabolic control on HRQoL, with specific regard to physical and mental component summaries. Our hypothesis was that anxiety may negatively affect HRQoL, with special regard to mental well-being, while diabetes duration and metabolic control may impact on physical well-being.

MATERIALS AND METHODS

Participants

The study was conducted on a group of 45 patients, consecutively recruited at the Outpatients Clinics of the Department of Clinical and Experimental Medicine, University Hospital of Messina, Italy. Patients had a certified diagnosis of T2DM according to the American Diabetes Association criteria (American Diabetes Association., 2018). Inclusion criteria were: age ranging from 55 to 75 years; time since diagnosis of T2DM >5 years; oral treatment with hypoglycemic agent (metformin) at stabilized schedules in the last 12 months, to avoid confounders due to disease severity and related complications, usually associated with both insulin treatment and outcomes; a full screening for diabetic related complications over the last 6 months; Mini-Mental State Examination score (MMSE) >24, to overcome individuals unable to perform or understand the psychological scales. Exclusion criteria were: heart failure with New York Heart Association (NYHA) class >2; moderate and severe respiratory failure; moderate to severe kidney or liver failure; endocrine disorders other than DM (e.g., thyroid or parathyroid disease); severe musculoskeletal disease; cancer; cognitive impairment; neurologic or psychiatric condition or use of neuro-psychotropic drugs.

Ethics Statement

The study was approved by the Institutional Ethical Committee of the University Hospital "Gaetano Martino," University of Messina, Messina, Italy. All subjects were deeply informed about the research aim of the study and gave written informed consent in accordance with the Declaration of Helsinki and its later amendments. Participants were evaluated by clinical psychologists in collaboration with physicians. All intervention, including rating scales administration and HbA1c detection, were performed as a part of daily clinical practice assessment of patients. Data were analyzed anonymously.

Measures

Demographical and Medical Data

For each participant data were collected including age, gender, education, smoking habit, employment, and marital status, considered as categorical variables. Medical information comprised data on BMI, T2DM and related complications, time since T2DM diagnosis and metabolic control.

Clinical Psychological Evaluation

A gold standard diagnostic interview was performed by researcher in clinical psychology in a confidential setting, to detect patient's mental status (Fava et al., 2012). It was combined with the use of self-report measures. Particularly, the Hamilton Anxiety Rating Scale (HAM-A) was administered to measure anxiety levels. As known, HAM-A allows to detect both psychological and somatic symptoms, comprising anxious mood; tension; fears; insomnia; intellectual; depressed mood; somatic symptoms; sensory; cardiovascular; respiratory; gastrointestinal; genitourinary; autonomic and observed behavior at interview. Each of 14 items is scored from 0, not present, to 4, severe (Hamilton, 1959). The Beck Depression Inventory-second edition (BDI-II), comprising 21 items, was used to evaluate levels of depression, based on a total score derived from a scale of four points for each proposed item (Beck et al., 1996; Ghisi et al., 2006). The Italian version of the Short Form-36 (SF-36) survey was administered to measure patient's health perceived HRQoL (Ware and Sherbourne, 1992; Apolone and Mosconi, 1998). It consists of eight multi-items scales assessing *mental health* (reflecting emotional well-being), *role emotional* (reflecting limitations due to emotional health problems), *social functioning*, *vitality*, *general health*, *bodily pain*, *role physical* (reflecting limitations due to physical problems, *physical functioning*. This self-report scale assesses health status via two subscales: Physical Component Summary (PCS) which detects physical well-being and Mental Component Summary (MCS) which captures mental well-being. The SF-36 possible score ranges from 0 to 100 points, with higher scores indicating a better HRQoL. The scoring algorithm for MCS comprises positive weights for vitality, social functioning, role emotional, and emotional well-being scales, and negative weights for the physical functioning, role physical, bodily pain and general health scales. Whereas, the scoring algorithm for PCS covers positive weights for the physical functioning, role physical, bodily pain, general health and vitality scales and negative weights for the social functioning, role emotional, and emotional well-being scales.

Clinical Characteristics

Physical evaluation was conducted measuring height and weight, according to standard procedures, and BMI was calculated as weight in kilograms divided by the square of height in meters (Kg/m^2). Metabolic control was assessed trough the detection of glycated hemoglobin (HbA1c) expressed as per cent value (%), which reflects the mean blood glucose concentration in the last 3 months. T2DM related complications, macro- and microvascular diseases, sensory-motor neuropathy (i.e., hypertension and atherosclerosis nephropathy, retinopathy, glaucoma, and neuropathy) and T2DM related pharmacological treatment were obtained from the patients' medical records.

Statistical Analysis

Statistical analyses were performed using MedCalc software (version 10.2.0.0; Mariakerke, 173 Belgium). Kolmogorov-Smirnov test was used to test the normality of distribution of continuous variable. Student's *t*-test for unpaired observations or Mann-Whitney test were applied. The degree of the association between two variables was analyzed with Spearman's correlation coefficient. Multiple regression analysis was performed to evaluate the relationship between a dependent variable and one or more independent variables. Values of $p < 0.05$ were considered to indicate statistical significance.

RESULTS

The recruited 45 participants were predominantly female (70%) and reported a mean age of 65.3 ± 5.9 years. All patients were Caucasian, resident in the South of Italy. The clinical sample characteristics are showed in **Table 1**.

Most of the participants had graduated from secondary school (41%) and resulted to be currently married (67%). With regard to the employment status, 44% was represented by pensioner and 44% by housewife, while only 12% was full time. Time since T2DM diagnosis showed a mean value of 11.6 ± 6.7 years. All patients were treated with oral hypoglycemic agents (metformin), showing a good glycemic control and only 40% of them reported T2DM related outcomes, as showed in **Table 1**.

With regard to the clinical psychological investigation, mainly conducted with the gold standard diagnostic interview, it has been specifically excluded any psychiatric condition. Participants showed moderate depressive symptoms as resulted by median BDI-II score of 13(8.3–21.4), while median HAM-A score [25(20.7–30.6)], considering both somatic and psychic anxiety, was representative of a high prevalence of anxious symptoms in the recruited subjects. **Table 2** shows SF-36 scores.

As observed both PCS and MCS showed a lower perceived HRQoL in the clinical sample (**Figure 1**).

Particularly the lowest scores have been detected in the *role emotional* and *bodily pain* dimensions, while *physical* and *social functioning* showed the highest scores. **Figure 1** shows the distribution of *Physical and Mental Component Summary* scores in the clinical sample. **Figure 2** shows the median *Physical and Mental Component Summary* scores according to HAM-A values.

TABLE 1 | Demographic and medical characteristics of the study sample.

Variables		Clinical sample (n = 45)
Gender	M	30%
	F	70%
Education	Primary school	38%
	Secondary school	41%
	High school	11%
	Bachelors's degree	6%
	Ph D or specialization	4%
Employment status	Housewife	44%
	Full time	12%
	Unemployed	0
	Pensioner	44%
Marital status	Never married	6%
	Currently married	67%
	Widowed	15%
	Cohabitant	6%
	Separated or divorced	6%
T2DM time since diagnosis (yrs)		11.6 ± 6.7
HbA1c (%)		7.1 ± 0.9
T2DM related complications	Micro-vascular diseases	15%
	Macro-vascular diseases	15%
	Macro + Micro	5%
	Sensory motor neuropathy	5%
Age (yrs)		65.3 ± 5.9
BMI (Kg/m^2)		29.9 ± 5.2
Current smoking		15%

Values are expressed as mean ± SD. HbA1c, glycated haemoglobin; T2DM, type 2 diabetes mellitus; BMI, body mass Index.

TABLE 2 | Measurements of health related quality of life (HRQoL) measured by the Short Form-36 (SF-36) questionnaire.

SF-36 variable	Clinical sample median (IQR)
Mental health	60 (51.7 – 72)
Role emotional	33 (0 – 66)
Social functioning	62 (50 – 62.7)
Vitality	40 (34.7 – 60)
General health	40 (35 – 42.2)
Bodily pain	30 (21.8 – 41.6)
Role physical	50 (0 – 50)
Physical functioning	75 (64.7 – 80.3)
Physical component summary (PCS)	38 (33.9 – 41.1)
Mental component summary (MCS)	36 (32 – 45.2)

All the SF-36 dimensions were inversely and significantly related with anxious and depressive symptoms, except *role physical* and *general health*, as showed in **Table 3**. Moreover *vitality* was inversely and significantly related to metabolic control. Time since T2DM diagnosis was negatively associated to *physical functioning* and PCS and individuals' age was inversely related to both *role physical* and *physical functioning* (**Table 3**).

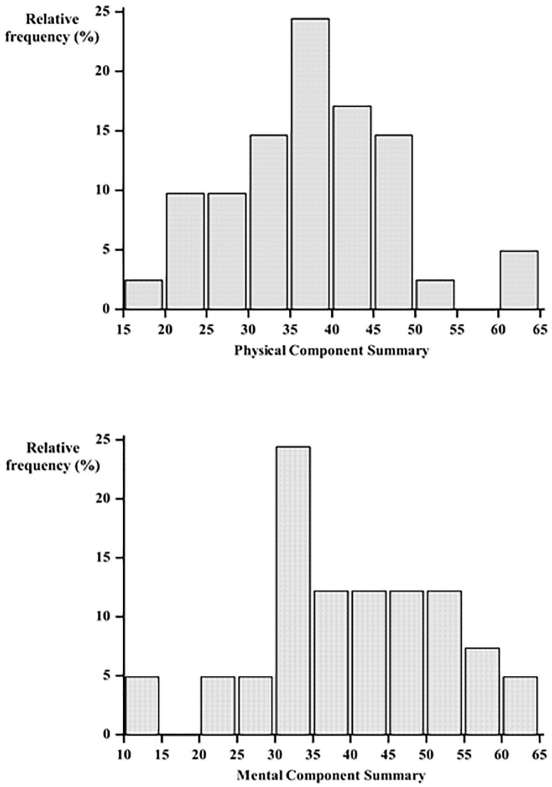

FIGURE 1 | Distribution of Physical Component Summary (PCS) and Mental Component summary (MCS) measured by the Short Form-36 (SF-36).

Neither anxiety nor depression were associated with metabolic control and time since diagnosis ($p > 0.05$). Participants with higher education level showed a better but not significant metabolic control in comparison with participants with lower education level [HbA1c 6.9(6.6–7.3) vs. 7.2(6.8–8.8), $p = 0.08$]. Socio-demographic variables, as gender, employment status, marital status and current smoking habit were not significantly associated neither with metabolic control, nor with psychological features.

A multiple regression analysis, after correcting for age, BMI, HbA1c value and BDI-II score, showed that the PCS was significantly related to both time since diagnosis ($\beta = -0.55$, $p = 0.03$, $SE = 0.25$) and HAM-A scores ($\beta = -0.52$, $p = 0.04$, $SE = 0.24$). Moreover, after correcting for age, BMI, HbA1c value and T2DM time since diagnosis, both HAM-A ($\beta = -0.67$, $p = 0.01$, $SE = 0.26$) and BDI-II ($\beta = -0.48$, $p = 0.02$, $SE = 0.20$) scores were independently predictive of MCS (as showed in **Figure 3**). Metabolic control, instead, was not a significant predictor of HRQoL.

DISCUSSION

The current study is the first original report aiming to explore the relationship between PCS, MCS, anxious and depressive symptoms, time since diagnosis and metabolic control, in

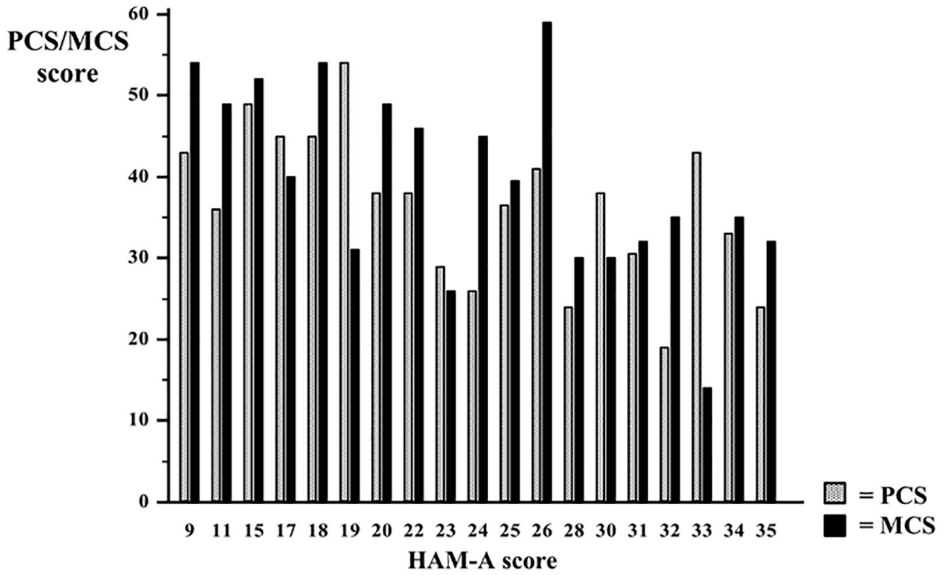

FIGURE 2 | Median Physical Component Summary (PCS) and Mental Component summary (MCS) values according to HAM-A score.

TABLE 3 | Correlation coefficients (*r*) between studied variables.

SF-36	Age	BMI	Time since diagnosis	HbA1c	HAM-A score	BDI-II score
Mental health	−0.15	−0.09	−0.02	0.04	**−0.58**	**−0.48**
Role emotional	−0.25	−0.18	0.03	−0.05	**−0.40**	**−0.55**
Social functioning	−0.05	**−0.5**	−0.19	−0.12	**−0.48**	**−0.37**
Vitality	0.10	−0.17	−0.09	**−0.4**	**−0.65**	**−0.36**
General health	0.05	0.12	−0.16	−0.02	**−0.48**	−0.25
Bodily pain	−0.02	−0.15	−0.20	−0.16	**−0.65**	**−0.49**
Role physical	**−0.32**	−0.30	−0.25	0.05	−0.21	−0.21
Physical functioning	**−0.38**	−0.03	**−0.31**	−0.10	**−0.43**	**−0.46**
Physical component summary	−0.10	−0.15	**−0.33**	−0.18	**−0.44**	−0.24
Mental component summary	−0.07	−0.19	0.01	−0.13	**−0.53**	**−0.45**

BMI, body mass index; HbA1c, glycated haemoglobin. Statistical significant values of "r" ($p < 0.05$) are shown in bold.

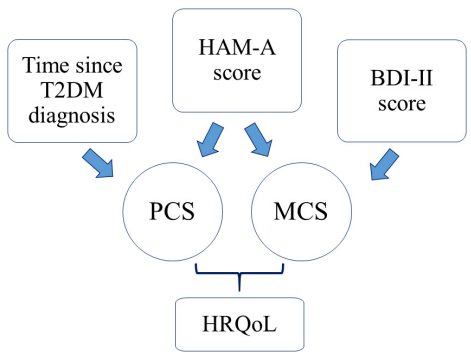

FIGURE 3 | Main determinants of HRQoL in T2DM patients.

patients with T2DM. Our findings suggest anxiety negatively affects the HRQoL in patients with diabetes of long duration. Anxious symptoms are frequent features in T2DM, which is a chronic progressive condition with physical and psychological concerns (Anderson et al., 2002; Amiri and Behnezhad, 2019). A large population based study showed that people with T2DM had a 20% higher prevalence of life-time diagnosis of anxiety than those without, after adjustment for BMI, educational level, marital and employment status, and current smoking habit (Li et al., 2008). Some explanations about the association between anxiety and diabetes have been proposed (Smith et al., 2013). In fact, it has been reported that a chronic illness such diabetes could lead to an increased risk to develop anxious symptoms, due to both physical symptoms-related worries and disease progression concerns (Goldbacher and Matthews, 2007). It is known that T2DM may provoke distress, as patients are required to self-manage a such chronic disease, frequently measuring blood glucose levels, addressing follow-up with adequate adherence (Marchini et al., 2018). This is also corroborated by Marshall et al. (1997) relatively to psychological distress which may lead to unhealthy behavior impairing compliance and adherence. On the other hand,

in a large prospective population-based study, investigating the associations between depression, anxious symptoms and diabetes, individuals with such psychopathological features showed an increased risk of T2DM onset at 10-year follow-up, independently of established risk factors for DM (Engum, 2007; Shinkov et al., 2018). Moreover, the comorbidity of anxiety and T2DM could be due to common factors as pain, complications, un-healthy self-care behaviors, depression and BMI (Engum, 2007; Settineri et al., 2019; Rosa et al., 2019). With regard to the possible pathogenic association between anxiety and T2DM, it has been reported that the development of DM may be due to the stress-induced cortisol release in inflammatory response, even mediated by anxiety (Kiecolt-Glaser et al., 2002; Black, 2003; Seematter et al., 2004; Stellar et al., 2015; Conti et al., 2016). This evidence has been observed in several medical conditions, as cardiovascular and musculoskeletal diseases (Godsland et al., 1998; Catalano et al., 2017).

Particularly, physical outcomes could impair HRQoL as T2DM involves a possible distress related to the long-life self-management, which requires long term follow-up to both ensure metabolic control and to avoid complications. On the other side, anxiety and emotional distress could impair perceived HRQoL, with special reference to the limitations due to emotional problems, which could in turn provoke misadjustment in DM self-care.

Nguyen et al. (2018) found that older age and a longer duration of diabetes were negatively associated with the EQ-5D index, used to evaluate HRQoL. In accordance, we found that time since T2DM diagnosis was strictly related to HRQoL; mainly time since diagnosis was negatively associated to physical functioning and PCS and individuals' age was inversely related to both role physical and physical functioning.

To properly follow T2DM self-management it could be fundamental patients psychologically to elaborate their chronic illness to find the best adaptive adjustment through self-management strategies. Moreover, such long duration disease may provoke important limitations and impairment of individuals' life-style. Mainly, T2DM can be also associated to psychopathological symptoms, as occurs in other several chronic conditions, which could impact HRQoL too (Engum, 2007; Crincoli et al., 2016; Catalano et al., 2018). We hypothesized that anxiety, concurring with T2DM features, times since diagnosis and metabolic control, may impair HRQoL and our findings confirmed the significant and negative anxiety association with all SF-36 domains, except role physical, and particularly with mental health, role emotional, social functioning, vitality, general health, bodily pain, physical functioning, PCS and MCS. It could be interesting to comprehend the strictly role of anxiety and T2DM as predictors of lower HRQoL, and mostly on the specific explored dimensions. In our study HRQoL investigation has been carried out including the global SF-36 questionnaire administration, allowing researchers to study the perceived HRQoL regardless of confounders. Mainly, the summarized indexes we investigated, PCS and MCS, have been analyzed in association with time since diagnosis, metabolic control as resulted by HbA1c, and with anxiety levels as resulted by HAM-A scores. We even hypothesized the role of anxious symptoms on MCS and the prevalent impact of metabolic control and diabetes duration on PCS. Our results partially disconfirmed this hypothesis suggesting that anxiety significantly impacts on HRQoL, with regard to both PCS and MCS, but indicated also that diabetes duration, but not metabolic control, impairs on PCS. Moreover, metabolic control does not significantly impair HRQoL dimensions, independently from time since diagnosis, probably due to the recruited clinical sample which was characterized by a good metabolic control, as resulted by HbA1c values almost in therapeutic range. With reference to anxiety levels and its impact on PCS, we could speculate that anxious individuals develop unconscious inhibition and avoiding attitude to perform physical activities, as results from the higher limitations due to physical problems. This theoretical psychodynamic mechanism does not concern depressive symptoms, as demonstrated by the not significant association between depression and PCS, at the linear regression analysis. In our clinical sample depressive symptoms were significantly and inversely associated with mental health, role emotional, social functioning, vitality, bodily pain, physical functioning, and MCS. Furthermore, at a multiple regression analysis, BDI-II score was independently predictive of HRQoL. This data could suggest that even depression, as well as anxiety, significantly and independently impacts on perceived HRQoL in T2DM. Stanton and Hoyt (2017) reported patients with longer time since diagnosis may develop a better adjustment to this chronic disease and to its self-management. Conversely, our findings demonstrated that longer time since diagnosis is predictive of lower HRQoL, with specific reference to PCS and regardless to outcomes. This may be at list in part explained with the underlined psychological features involving emotional stress. Thus, in future researches it could be valuable to plan a clinical psychological intervention strategy, supporting patient to psychologically elaborate and integrate such chronic illness, aimed to a healthier life-style and a better perceived HRQoL, which may also reduce long-life outcomes and complications. This psychological approach, focused on such fundamental issue, could add more qualitative data, even according to a case study approach (Langher et al., 2017). This raise the main role of underlying symbolic and less conscious dynamics, which may include several implications in care relationships (Caputo, 2013; Nazzaro et al., 2017; Tomai et al., 2017).

The strengths of the current study include the multiple regression analysis which allowed us to define the impact of anxiety on HRQoL after multiple adjustment as depressive symptoms, time since diagnosis and metabolic control. Moreover we added to the self-report measures a gold standard as a diagnostic interview, conferring a specific objectivity to the surveys carried out.

Limitations of our study include the cross sectional design, the small sample size and the casual prevalent female gender, which didn't allow us to observe sub-group analysis (i.e., gender, exercises) which is, however, what we aim to perform as our main perspective research. Other limitations are: the oral anti-diabetic treatment represented by metformin, which conferred on the other side homogeneity to the sample; the use of BDI-II even if there are many depression inventories validated in diabetes cohorts, which is due to a general standardized evaluation for outpatients referring to our Department for chronic diseases.

CONCLUSION

Our study suggests a predictive role of both anxiety levels and time since diagnosis in HRQoL in a chronic disease such as T2DM. Our findings highlighted that higher PCS levels, expression of a better HRQoL with regard to physical component, were associated to lower anxiety levels and less time passed since T2DM diagnosis. Moreover, higher MCS levels, expression of a better HRQoL with regard to mental component, were associated to lower anxious and depressive symptoms but not with diabetes duration or metabolic control. These data could be useful to plan T2DM psychological intervention focused on psychological health concerns, leading to a healthy self-management and a better HRQoL, even assisting patients in reducing the psychological and physic outcomes due to the T2DM long duration.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

GM made significant contribution to design the research study, to draft the manuscript and to provide the interpretation of data. AC performed the statistical analysis by providing the interpretation of data and provided significant contribution to draft part of the manuscript. FB, GR, and AL provided substantial contribution in drafting part of the manuscript. CV and MQ revised the article critically. NM gave the final approval of the version of the manuscript to be submitted.

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Alexithymia and Psychological Distress in Patients With Fibromyalgia and Rheumatic Disease

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Background: Fibromyalgia syndrome (FMS) is a chronic rheumatologic disease characterized by widespread musculoskeletal pain and other psychopathological symptoms which have a negative impact on patients' quality of life. FMS is frequently associated with alexithymia, a multidimensional construct characterized by difficulty in identifying feelings (DIF) and verbally communicating them difficulty describing feelings (DDF) and an externally oriented cognitive thinking style (EOT). The aim of the present study was to investigate the relationship between alexithymia, anxious and depressive symptoms and pain perception, in patients with FMS and other rheumatic diseases (RD).

Methods: The sample consisted of 127 participants (M = 25, F = 102; mean age: 51.97; SD: 11.14), of which 48 with FMS, 41 with RD and 38 healthy control group (HC). All groups underwent to a test battery investigating anxiety and depressive symptoms (HADS), pain (VAS; QUID-S/-A) and alexithymia (TAS-20).

Results: A high prevalence of alexithymia (TAS $\geq$ 61) was found in FMS (47.9%) and RD (41.5%) patients, compared to the HC group (2.6%). FMS patients showed significant higher scores than HC on DIF, DDF, EOT, anxiety and depression. The clinical sample, FMS and RD groups combined (n = 89), alexithymic patients (AL, n = 40) exhibited higher scores in pain and psychological distress compared to non-alexithymic patients (N-AL, n = 34). Regression analysis found no relationship between alexithymia and pain in AL, meanwhile pain intensity was predicted by anxiety in N-AL.

Conclusion: While increasing clinical symptoms (pain intensity and experience, alexithymia, anxiety, and depression) in patients with fibromyalgia or rheumatic diseases, correlations were found on the one side, between alexithymia and psychological distress, on the other side, between pain experience and intensity. Meanwhile, when symptoms of psychological distress and alexithymia were subthreshold, correlations with pain experience and intensity became stronger.

Keywords: chronic pain, fibromyalgia, alexithymia, rheumatoid arthritis, depression, anxiety

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INTRODUCTION

Fibromyalgia syndrome (FMS) is a chronic condition characterized by widespread musculoskeletal pain, tenderness of the muscles, stiffness and extra-articular symptoms such as fatigue, anxiety, sleep disorders depression and functional impairment of daily living activities (Gerdle et al., 2008; Jahan et al., 2012). These factors may negatively influence the quality of life of the individuals affected. An increasing number of studies have examined patients' experiences of illness across a variety of chronic conditions, amongst others, osteoporosis (Catalano et al., 2018; Martino et al., 2018a,b), diabetes (Marchini et al., 2018; Settineri et al., 2019), chronic pain (Catalano et al., 2017) and FMS (Verbunt et al., 2008; Lee et al., 2017) using comprehensive health-related quality of life questionnaires or other outcomes measures provided by the clinical research (Coin et al., 2009) in order to evaluate the burden of diseases, which could be used for treatment planning and monitoring of syndrome progression.

In the context of fibromyalgia, several studies have shown that fibromyalgia is a widespread condition, commonly occurring in young or middle-aged females and the prevalence in the general population is between 0.5 and 5% (Branco et al., 2010).

Despite the increasing knowledge about FMS, the etiopathogenesis of the disease is still unclear. Many factors seem to be involved: genetic, immunological, hormonal, psychological and environmental (Bellato et al., 2012; Albrecht et al., 2019; Atzeni et al., 2019). Central sensitization mechanisms and pain neuromodulation seem to play a primary role in FMS symptoms (Bellato et al., 2012). Among all rheumatic pathologies, FMS is ranked as second for level of diffusion, after osteoarthritis (Clauw, 2014) with a male/female ratio of 1:9 (Bartels et al., 2009). FMS symptoms can vary and are similar to those of several other conditions and the absence of specific laboratory tests or biomarkers make the diagnostic process rather complex. In order to overcome to the mentioned limitations, the American College of Rheumatology (ACR) has approved quantitatively validated classification criteria for FMS which are the most commonly used in clinical and therapeutic research as follows: (1) Generalized pain, defined as pain present in at least 4 of 5 body regions; (2) specific Widespread Pain Index (WPI) and Symptom Severity Scale (SSS): WPI $\geq$ 7 e SSS $\geq$ 5 or 6 $\geq$ WPI $\geq$ 4 e SSS $\geq$ 9; (3) symptoms have been present for at least 3 months; (4) FMS diagnosis is valid even in the presence of other diagnoses and doesn't exclude the presence of other illnesses (Wolfe et al., 2016).

Chronic and diffuse pain seems to be the core symptom of FMS, is associated with a high sensitivity to touch, a lowering of pain threshold, headache, gastrointestinal disorders and severe fatigue (Wallace and Hallegua, 2004; Marcus et al., 2005; Russell and Raphael, 2008; Wolfe and Häuser, 2011; Giamberardino et al., 2016; Doerr et al., 2017). Sleep disorders are also common among FMS patients and are characterized by difficulty in falling asleep, frequent nocturnal awakenings and non-restorative sleep (Palagini et al., 2016; Roth et al., 2016). Furthermore, many studies have reported a high prevalence of cognitive symptoms compared to other rheumatic diseases (RD) (Katz et al., 2004; Gelonch et al., 2017); in particular, a triad of cognitive disturbances (concentration difficulties, short-term memory problems, difficulty in multitasking) and a state of mental confusion termed "fibro-fog" (Katz and Leavitt, 2014) is often present.

Additionally, FMS in females seems to be associated with sexual dysfunctions, such as decreased sexual desire and the presence of pain during sexual intercourse, though psychiatric comorbidity may have more influence on sexual satisfaction than the presence of the rheumatic disease itself (Kalichman, 2009; Yilmaz et al., 2012; Bazzichi et al., 2013; Matarin Jimenez et al., 2017).

Psychiatric disorders such as depression, anxiety, obsessive-compulsive disorder and post-traumatic stress disorder are frequently comorbid with FMS (Henningsen et al., 2003; Dell'Osso et al., 2011; Clauw, 2014; Løge-Hagen et al., 2018; Conversano et al., 2019). The most common comorbidities are mood disorders, with a prevalence of 29–34.8% and anxiety disorders, with a prevalence of 22.3–32.2%; indeed, a careful screening of depressive and anxiety symptoms and their proper management is a primary target in FMS (Epstein et al., 1999; Thieme et al., 2004; Uguz et al., 2010; Piccinni et al., 2011; Consoli et al., 2012; Veltri et al., 2012; Davis et al., 2014; Kudlow et al., 2015). Several studies also highlight the presence of variables associated with psychological vulnerability such as low self-esteem, neuroticism, dependency, passivity, victimization, catastrophization, irritability and maladaptive response to loss (Hassett et al., 2000; Bradley, 2005; Conversano et al., 2010, 2018a,b; Carmassi et al., 2014; Bucourt et al., 2017). Fibromyalgia may indeed negatively affect daily life and mood, consequently inducing feelings of hopelessness, sadness, anger, anxiety or stress. Evidence also suggests that intense negative emotions accompanied by no foreseeable change for the future may lead to mental pain (Verrocchio et al., 2016).

Chronic pain conditions seem to be associated with the presence of alexithymic traits, in particular disorders such as chronic low back pain, FMS, temporomandibular pain and myofascial pain syndrome (Ak et al., 2004; Sayar et al., 2004; Celikel and Saatcioglu, 2006; Lumley et al., 2007; Saariaho et al., 2017). Some studies show that alexithymia is common in FMS patients (Celikel and Saatcioglu, 2006; Taskin et al., 2007; Castelli et al., 2012; Di Tella et al., 2018; Aaron et al., 2019), although others report no differences in alexithymia scores in FMS patients versus healthy controls (Malt et al., 2002). Alexithymia is a complex, multidimensional psychological construct that describes both a difficulty in cognitive processing of emotional experience and a deficit in emotional regulation (Taylor et al., 1997). This construct, which literally means "lack of words to describe emotions," was first introduced by Sifneos in 1972 to describe people who were unable to communicate their feelings and had poor imaginative abilities and who often presented a series of somatic symptoms. The main aspects of alexithymia are the following: difficulty identifying and describing emotions and feelings, difficulty distinguishing between emotions and body associated sensations and a cognitive style which is practically oriented, with a paucity of imaginative processes (Taylor et al., 1997). High levels of alexithymia seem to prevent a correct emotional regulation, especially regarding negative

emotions, and to cause a chronic physiological hyperactivation, physical symptoms and somatic amplifications (Lumley et al., 1996). Individuals showing high levels of alexithymia not only have limited ability to reflect and regulate their emotions, but also struggle to verbally communicate them (Taylor, 2000; Torrado et al., 2018).

The theoretical stance that alexithymia is a personological trait characterized by a deficit of regulation and emotional processing, has made this construct particularly useful in exploring the role of personality and emotions in the pathogenesis of different somatic diseases (Taylor, 2000). Associations between alexithymia and different somatic pathologies such as chronic intestinal inflammatory diseases (Porcelli et al., 1996; Mazaheri et al., 2012), chronic respiratory disorders (Serrano et al., 2006; Baiardini et al., 2011), dermatological conditions (Willemsen et al., 2008; Talamonti et al., 2016) and neuromuscular pathologies (Hosoi et al., 2010) are reported frequently in the literature. However, it has been highlighted that alexithymia can also manifest as a transient state that varies in severity in accordance with stress levels and the presence of psychopathological conditions, including depression and anxiety disorders (Honkalampi et al., 2000; Pollatos et al., 2011; Montoro et al., 2016).

Overall the presence of alexithymia in patients with chronic pain and its influence on pain intensity is still unclear: many studies haven't found significant associations (Cox et al., 1994; Evren et al., 2006), while others found only weak correlations (Lumley et al., 2005a,b; Celikel and Saatcioglu, 2006) and in some studies this relationship appeared to be mediated by negative affect, especially depression (Di Tella and Castelli, 2016; Aaron et al., 2019). Castelli et al. (2012) have shown positive associations between alexithymia and the affective experience of pain, anxiety, depression, QoL and neuroticism. A recent study (Di Tella et al., 2017) has shown the presence of higher levels of pain symptoms and psychological distress in alexithymic FMS patients compared to non-alexithymic ones. Moreover, the results of the study highlighted a positive association between alexithymia, particularly between difficult in identifying feelings, and the affective dimension of pain experience, supporting the hypothesis that in patients with chronic muscular disease, alexithymia is more related to the unpleasant affective dimension of pain than the sensorial one. The association between alexithymia and pain was specifically mediated by anxiety.

Several studies have pointed out that differences in levels of alexithymia of FMS and healthy controls significantly decrease or disappear once anxiety and depression are statistically controlled, supporting the view that alexithymia may represent a state phenomenon that varies in relation to severity of clinical symptoms (Steinweg et al., 2011; Marchesi et al., 2014; Montoro et al., 2016). Montoro et al. (2016) showed that alexithymia was more closely associated with clinical variables (pain, fatigue, sleep, anxiety, depression, QoL) in healthy subjects than in FMS group in which many associations disappeared when anxiety and depression were controlled.

Therefore, the precise role of alexithymia in fibromyalgia has not yet been clarified. The present work aims to investigate and clarify the relationship between alexithymia, pain, anxiety and depression in FMS patients. The first aim is to further evaluate alexithymia in FMS patients, in comparison with healthy subjects and patients with other chronic pain pathologies, such as arthritis, and to explore its relationship with pain perception and other psychological factors, such as emotional distress (anxiety and depression). The second aim is to verify whether alexithymia is related to pain perception (in its sensory and affective components) and pain intensity, and to what extent psychological distress, especially anxiety and depression, is involved in this relationship.

According to previous researches, we hypothesized that FMS and RD patients would exhibit higher levels of alexithymia, pain perception, anxiety and depression while compared with HC. We also hypothesized that alexithymia might influence pain affective dimension, as it might be a state phenomenon that varies in relation to severity of anxious and depressive symptoms.

MATERIALS AND METHODS

Participants' Inclusion/Exclusion Criteria

One hundred and twenty-seven subjects with a mean age of 51.97 years (SD = 11.14) were recruited for the study. Chronic pain patients were recruited between May and December 2018 at the University of Pisa Hospital's Rheumatology Unit (A.O.U.P). The clinical sample consisted of two groups: patients with a diagnosis of either FMS (n = 48), according the ACR criteria (Wolfe et al., 2011), or rheumatic disease (RD; n = 41). All patients had a main diagnosis, made by an expert rheumatologist. The exclusion criteria for both groups were: age below 18, education level below 5 years, insufficient knowledge of Italian language and presence of an important neurological and/or psychiatric disorder.

The healthy control group (HC; n = 38) was recruited from patients' partners or relatives that accompanied them to visit. They had no history of chronic pain and met the same exclusion criteria.

Ethics

The study was approved by Hospital of Pisa Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All participants gave their written informed consent before participating in the study.

Materials

Alexithymia

The Italian version of the Toronto Alexithymia Scale (TAS-20; Bressi et al., 1996) was used to assess alexithymia. This is a self-administered questionnaire consisting of 20 items scored on a 5-point Likert scale recording respondents degree of agreement/disagreement for each statement (1 = I don't agree at all; 2 = I don't agree very much; 3 = I'm not either neither agree nor disagree; 4 = I agree in part; 5 = I completely agree). TAS-20 has three subscales representing three main facets of alexithymia: the Difficulty Identifying Feelings (DIF, seven items) subscale, measures difficulties

in distinguishing between specific emotions and/or bodily sensations related to emotional arousal; the Difficulty Describing Feelings (DDF, five items) subscale, indicates inability to verbalize one's experienced emotions; the Externally Oriented Thinking (EOT, eight items) subscale, indicates the tendency to focus attention externally instead of considering inner emotional experience. A global score ranging between 20 and 100 is calculated as a sum of the three subscales and there are cut-off points as following: alexithymia, TAS $\geq$ 61; borderline, 52 < TAS < 61; no alexithymia, TAS $\leq$ 51. It is the most widely used instrument both in clinical and research for the evaluation of alexithymia and it has good internal consistency (Cronbach's alpha = 0.81) and good test–retest reliability (0.77, $p < 0.01$) (Bagby et al., 1994a,b; Parker et al., 2003; Taylor et al., 2003).

Pain Evaluation

Pain intensity

The Visual Analog Scale for Pain was used to assess pain intensity (VAS; McCormack et al., 1988). The VAS is a single item scale and consists of a 10 cm horizontal line on which the subject had to indicate the average intensity of pain experienced in the previous week: the scale ranges from 0 ("no pain") to 10 ("extreme pain"). VAS is widely used due to its simplicity and adaptability to various settings and populations; it has been used in different populations, including those with RD (Huskisson, 1974; Downie et al., 1978). The scale showed good statistical qualities both for the evaluation of chronic pain and for experimental scopes (Price et al., 1983), Test–retest reliability has been shown to be good ($r = 0.94$, $p < 0.001$) (Ferraz et al., 1990).

Pain experience

The Questionario Italiano sul Dolore, the Italian adaptation of the McGill Pain Questionnaire (Melzack, 1975) was administered to evaluate pain experience (QUID; De Benedittis et al., 1988). It is a self-administered questionnaire that asks subjects to choose adjectives from 16 subclasses to describe the pain experienced during the previous month. These adjectives belong to four categories: sensory, which describes pain in terms of spatial and temporal properties; affective, referred to the affective qualities of pain such as tension, fear, autonomic reactions; evaluative, which reports the overall subjective impression on the painful experience and mixed that combines different sensory, affective and evaluative aspects. Only the sensory (QUID-S) and affective (QUID-A) components of pain experience were considered for the purposes of the present study. Test–retest reliability in population with a variety of conditions including arthritis and other musculoskeletal conditions was good ($r = 0.70$) (Melzack, 1975; Love et al., 1989; Broderick et al., 2008).

Psychological Distress

To assess symptoms of psychological distress, the Italian adaptation of the Hospital Anxiety and Depression Scale was used (HADS; Zigmond and Snaith, 1983; Costantini et al., 1999). This instrument consists of 14 items scored on a 3-point Likert scale divided into two subscales: anxiety (HADS-A) and depression (HADS-D), both composed of seven items. Subscales score ranges from 0 to 21 and cut-off points are the following: normal, HADS-A or HADS-D $\leq$ 7; borderline/abnormal level of anxiety or depression, 8 $\leq$ HADS-A or HADS-D $\leq$ 10; clinically relevant level of depression or anxiety, 11 $\leq$ HADS-A or HADS-D $\leq$ 21 (Zigmond and Snaith, 1983). Cronbach's alpha for HADS-A varied from 0.68 to 0.93 (mean 0.83) and for HADS-D from 0.67 to 0.90 (mean 0.82) (Bjelland et al., 2002).

Statistical Analysis

Distributions were assessed using the Kolmogorov–Smirnov test. All clinical variables for FMS, RD and HC groups were not normally distributed, and so the data were analyzed using Kruskal-Wallis with Dunn's multiple comparisons. Spearman's correlation was computed to evaluate the relationship between alexithymia, pain perception and intensity, anxiety and depression. Partial correlations were performed to control anxiety and depression effects. All clinical variables were normally distributed in the Alexithymia and No Alexithymia subgroups: *t*-test for independent samples was used to assess differences between subgroups. Pearson's coefficient was computed to evaluate variables correlations and multivariate linear regression was performed. *P* values <0.05 were considered statistically significant. The analysis was conducted using IBM SPSS statistics version 25.

RESULTS

Demographic Characteristics and Group Differences in Clinical Variables

A sample of 48 patients with FMS diagnosis (M = 1; age mean: 52.94; SD: 11.50), 41 patients with rheumatic disease diagnosis (M = 10; age mean: 54.74; SD:10.77) and a control group of 38 healthy subjects (M = 14; age mean: 47.92; SD:10.15) were included in the present study. Demographic characteristics are summarized in **Table 1**.

TAS $\geq$ 61 was found in FMS (47.9%) and RD (41.5%) patients, compared to the HC group (2.6%). Subjects in the FMS group reported significant higher scores than HC on TAS total score ($p < 0.0001$) (**Table 2**): particularly, FMS patients have higher scores on DIF ($p < 0.0001$), DDF ($p < 0.0003$) and EOT ($p < 0.01$) than healthy subjects. The same results were found comparing RD vs. HC groups.

58.3% of FMS patients and 48.8% of RD patients showed higher scores on HADS-A (HADS-A $\geq$ 8) and 66.7% of FMS patients and 51.2% of RD patients reported high scores on HADS-D (HADS-D $\geq$ 8) while only 5.3 and 13.2% of HC, reported scores above the cut-off on HADS-A and HADS-D, respectively. Patients in the FMS group showed significant higher scores than HC on HADS-A ($p < 0.0001$) and HADS-D ($p < 0.0001$), in the same way as RD patients did compared to HC (HADS-A, $p < 0.0001$; HADS-D, $p < 0.0001$). Differences in alexithymia and psychological distress did not differ between the FMS and RD groups.

Questionario Italiano sul Dolore subscales (QUID-S, QUID-A) and VAS scores were significantly higher in

TABLE 1 | Demographic characteristics and prevalence in FMS, RD and HC groups.

	FMS group *n* = 48			RD group *n* = 41			HC group *n* = 38		
	Mean (SD)	**Range**	***n* (%)**	**Mean (SD)**	**Range**	***n* (%)**	**Mean (SD)**	**Range**	***n* (%)**
Age	52.94 (11.50)	20–72		54.74 (10.77)	25–73		47.92 (10.15)	22–73	
Gender									
F			47 (97.9%)			31 (75.6%)			24 (63.2%)
M			1 (2.1%)			10 (24.4%)			14 (36.8%)
Education (years)	10.85 (3.15)	5–18		10.75 (4.03)	5–18		13.23 (4.19)	5–18	
Duration of illness (years)	9.02 (6.15)	1–28		11.64 (8.59)	1–36		–		
Alexithymia									
Alexithymic			23 (47.9%)			17 (41.5%)			1 (2.6%)
Non-Alexithymic			17 (35.4%)			17 (41.5%)			33 (86.8%)
Borderline			8 (16.7%)			7 (17.1%)			4 (10.5%)
Psychological distress									
HADS-A $\geq$ 8			28 (58.3%)			20 (48.8%)			2 (5.3%)
HADS-D $\geq$ 8			32 (66.7%)			21 (51.2%)			5 (13.2%)

FMS; fibromyalgia, RD; rheumatic disease diagnosis, HC; healthy subjects, HADS-A; Hamilton Anxiety and Depression Scale-Anxiety, HADS-D; Hamilton Anxiety and Depression Scale-Depression.

TABLE 2 | Questionnaire scales and subscales scores.

	FMS group *n* = 48	RD group *n* = 41	HC group *n* = 38	
	Median (interquartile range)			***P*-value**
Alexithymia-TAS-20				
DIF	22.00 (14.75–26.00)	17.00 (14.00–23.00)	11.00 (7.50–14.00)	< 0.0001
DDF	16.50 (10.75–19.00)	15.00 (12.00–17.00)	11.00 (8.00–14.75)	0.001
EOT	19.00 (15.75–22.00)	20.00 (16.00–22.00)	16.00 (14.00–18.00)	0.003
TAS	60.00 (46.75–68.00)	56.00 (47.00–64.00)	40.50 (32.25–48.00)	< 0.0001
Pain-QIUD				
QUID-S	0.33 (0.23–0.42)	0.30 (0.12–0.39)	0.03 (0.00–0.14)	< 0.0001
QUID-A	0.40 (0.27–0.53)	0.20 (0.07–0.40)	0.00 (0.00–0.18)	< 0.0001
VAS	7.00 (4.75–8.00)	5.00 (4.00–7.00)	1.00 (0.00–4.00)	< 0.0001
Psychological distress				
HADS-A	9.00 (6.00–13.00)	7.00 (4.00–11.00)	4.00 (2.00–5.00)	< 0.0001
HADS-D	9.00 (6.75–11)	8.00 (5.00–10.00)	3.00 (1.00–5.75)	< 0.0001

TAS-20; Toronto Alexithymia Scale-20 Item Version, DIF; Difficulty Identifying Feelings, DDF; Difficulty Describing Feelings, EOT; Externally-Oriented Thinking, TAS; TAS Total Score, QUID; Questionario Italiano sul Dolore, Sensorial Pain Rating Index (QUID-S), Affective Pain Rating Index (QUID-A), VAS; Visual Analog Scale for pain intensity, QUID-T; Total Pain Index, HADS-A; Hamilton Anxiety and Depression Scale-Anxiety, HADS-D; Hamilton Anxiety and Depression Scale-Depression. P values from Kruskal-Wallis non-parametric test.

subjects with FMS than HC. Moreover, FMS patients experienced a higher pain intensity ($p = 0.05$) than RD patients that is more characterized by the affective dimension of pain ($p = 0.013$).

Association Between Alexithymia, Pain and Psychological Distress in FMS, RD, and HC Groups

Correlation analysis conducted between alexithymia and other variables in FMS group (**Table 3**) showed a significant moderate positive association between DIF subscale and HADS-A ($r_s = 0.387$, $p = 0.007$). In this group, years of education was negatively correlated with DIF ($r_s = -0.331$, $p = 0.022$) and DDF ($r_s = -0.316$, $p = 0.029$) and both relationships were maintained while controlling for anxiety and depression. No significant correlations between alexithymia and pain were observed, meanwhile pain and psychological distress showed significant correlations.

Patients with RD exhibited significant moderate positive correlations between DIF and the QUID-S ($r_s = 0.453$, $p = 0.003$), QUID-A ($r_s = 0.466$, $p = 0.002$), VAS ($r_s = 0.480$, $p = 0.002$) and HADS-A ($r_s = 0.383$, $p = 0.014$). Furthermore, EOT was positively associated with HADS-D scores ($r_s = 0.341$, $p = 0.030$). Psychological distress and pain

TABLE 3 | Significant Spearman correlation coefficients: associations between alexithymia and questionnaire scores in patients with fibromyalgia (FMS), rheumatic diseases (RD) and healthy subjects (HC).

	FMS group *n* = 48	RD group *n* = 41	HC group *n* = 38
DIF			
QUID-S	0.261	**0.453****	**0.445****
QUID-A	0.111	**0.466****	**0.368***
VAS	0.163	**0.480****	**0.505*****
HADS-A	**0.387****	**0.383***	**0.493****
HADS-D	0.264	0.151	**0.411***
DDF			
QUID-S	0.211	0.296	0.239
QUID-A	−0.022	0.143	0.295
VAS	0.144	0.295	**0.322***
HADS-A	0.076	0.055	0.243
HADS-D	0.255	0.094	**0.504*****
EOT			
QUID-S	0.275	−0.147	**0.358***
QUID-A	0.209	−0.167	**0.380***
VAS	0.134	0.195	0.281
HADS-A	0.238	0.225	−0.006
HADS-D	0.102	**0.341***	0.248

*Same abbreviations as **Table 2**. Bold data indicate correlations that are significant. *p < 0.05; **p < 0.01; ***p < 0.001.*

showed significant correlations. While controlling for anxiety and depression in RD group, all the positive correlations between DIF and QUID-S and QUID-A were maintained. No significant associations with demographical variables such as age, years of education or duration of illness were observed in this group.

Alexithymia was more closely associated with psychological distress and pain in healthy subjects: DIF positively correlated with QUID-S (r_s = 0.445, p = 0.024), QUID-A (r_s = 0.368, p = 0.017), VAS (r_s = 0.505, p = 0.001), HADS-A (r_s = 0.493, p = 0.002) and HADS-D (r_s = 0.411, p = 0.011); DIF scores correlated with VAS (r_s = 0.322, p = 0.050) and HADS-D (r_s = 0.504, p = 0.001) while EOT is associated with QUID-S (r_s = 0.358, p = 0.028), QUID-A (r_s = 0.380, p = 0.019) and age (r_s = 0.420, p = 0.009). When anxiety and depression were controlled, positive correlations between DIF and VAS and between EOT and age were maintained.

Differences in Demographic Characteristics and Clinical Variables Between Patients With Alexithymia vs. No Alexithymia

In a clinical sample, the FMS and RD groups combined (n = 89), the total TAS score showed that 44.9% (40/89) patients had alexithymia (AL; TAS score ≥61), 38.2% (34/89) patients did not have aleithymia (N-AL; TAS-20 score ≤51) and 16.8% (15/89) patients were borderline (52 < TAS-20 < 61). Patients in the borderline group were excluded. AL and N-AL groups had no significant differences in age, education and duration of illness (**Table 4**).

Patients with alexithymia showed significant higher scores on HADS-A (p = 0.004), HADS-D (p = 0.007), VAS (p = 0.005) and QUID-S (p = 0.003) (**Table 5**).

Association Between Alexithymia, Pain and Psychological Distress in Patients With Alexithymia vs. No Alexithymia

Correlation analysis (**Table 6**) in the AL group showed that DIF and DDF were associated with HADS-A (p = 0.020) and HADS-D (p = 0.027), respectively. Meanwhile, VAS was related to the QUID-S (p < 0.0001) and QUID-A (p = 0.009) and these relationships were maintained when anxiety and depression effects were controlled. No significant relationship was found between alexithymia and pain in AL group, nevertheless, it was found in N-AL group (**Table 7**): EOT was positive associated with VAS (p = 0.049) and there's a trend of correlation between DIF and QUID-S (p = 0.066). DIF was negatively correlated with QUID-A (p = 0.05). Concerning psychological distress, HADS-A was negatively related to DIF (p = 0.010) and positively with EOT (p = 0.015); HADS-D was positively correlated with EOT (p = 0.033). All relationships were moderate.

In N-AL group, a significant regression model was obtained for VAS as the dependent variable and DIF, EOT, HADS-A, HADS-D and QUID-A as predictors, with a good level of fit with the data (R^2 = 0.53) (**Table 8**). HADS-A positively predict VAS (β = 0.381, p = 0.009). In AL group, VAS was predicted by QUID-S (β = 12.636, p < 0.0001) and the regression model explained the 50% of the variance of the data.

DISCUSSION

The main purpose of the research was to investigate the prevalence of psychological distress and alexithymia in fibromyalgia patients, compared to those suffering from arthritis and healthy controls. Moreover, we aimed to describe the role of these variables in pain perception (affective and sensory dimensions) and pain intensity.

The results showed higher levels of alexithymia in patients with fibromyalgia, arthritis and other painful rheumatic conditions compared with healthy controls, according to previous research (Steinweg et al., 2011; Baeza-Velasco et al., 2012; Montoro et al., 2016; Di Tella et al., 2017). Alexithymia scores were higher in all three TAS-20 dimensions. These results may highlight the presence of a greater difficulty in identifying and expressing emotions and an external oriented cognitive style in patients with chronic pain conditions compared to general population. No significant differences were found between the FMS and RD groups, suggesting that both chronic pain conditions may have similar impairment in awareness and emotional regulation.

In regard to psychological distress, we found comorbidities between painful chronic conditions and anxious or depressive clinical symptoms, matching previous studies (Dell'Osso et al., 2011; Clauw, 2014; Løge-Hagen et al., 2018; Conversano et al., 2019). Our clinical groups exhibited a greater psychological impairment compared to healthy controls, with higher levels

TABLE 4 | Demographic characteristics and prevalence in alexithymia vs. no alexithymia groups.

	Alexithymia *n* = 40			No alexithymia *n* = 34		
	Mean (SD)	**Range**	***n* (%)**	**Mean (SD)**	**Range**	***n* (%)**
Age	52,85 (12,67)	20–72		55.16 (8.99)	27–73	
Gender						
F			34 (85.0%)			32 (94.1%)
M			6 (15.0%)			2 (5.9%)
Education (years)	10.15 (3.64)	5–18		11.73 (3.63)	5–18	
Duration of illness (years)	9.06 (6.30)	1–24		12.00 (9.18)	1–36	
Psychological distress						
HADS-A ≥ 8			27 (67.5%)			14 (41.2%)
HADS-D ≥ 8			28 (70.0%)			16 (47.1%)

HADS-A; Hamilton Anxiety and Depression Scale-Anxiety, HADS-D; Hamilton Anxiety and Depression Scale-Depression.

of anxiety and depression, similarly to the ones reported in Castelli et al. (2012); 60% prevalence of depression (HADS-D) and a 52.7% of anxiety (HADS-A) in FMS group). Despite other studies reporting higher levels of depressive symptoms and psychological distress in the FMS group compared to other chronic rheumatologic disorders (Ozcetin et al., 2007; Piccinni et al., 2011; Scheidt et al., 2014), our findings showed that patients with FMS and RD displayed similar anxiety and depression levels. These discrepancies in results may be due to differences in samples characteristics, for example fibromyalgia patients treated with antidepressant therapies that have relieved clinical symptoms or to the use of different scales to measure psychological variables.

In agreement with Scheidt et al. (2014) results, fibromyalgia patients showed higher levels of pain intensity than RD patients. Moreover, FMS patients had higher scores than RD patients in the affective component of pain, in agreement with Di Tella et al. (2017). Both results are in consistent with the phenomenon of allodynia and pain sensitivity of the FMS syndrome: while FMS patients experienced an increased pain response to non-painful stimuli due to central sensitization, their pain perception seems to be more related to fear, tension and autonomic reaction to stimuli than RD patients.

TABLE 5 | Questionnaire scales and subscales scores in alexithymia vs. no alexithymia groups.

	Alexithymia *n* = 40	No alexithymia *n* = 34	*F*	*P* values
	Mean (SD)			
Pain				
QUID-S	0.34 (0.14)	0.24 (0.14)	0.043	**0.003**
QUID-A	0.37 (0.20)	0.28 (0.23)	0.881	0.064
VAS	6.75 (1.99)	5.18 (2.62)	3.147	**0.005**
Psychological distress				
HADS-A	10.00 (4.42)	7.15 (3.69)	0.841	**0.004**
HADS-D	9.28 (3.30)	7.03 (3.61)	0.466	**0.007**

*Same abbreviations as **Table 2**. P values from t-test for independent samples.*

Concerning associations between alexithymia and pain or psychological distress in FMS group, we found that alexithymia was not related to pain experience or intensity. This result suggest that lower emotional awareness does not play a primary role in pain perception, and it might be a transitional state related to severity of psychological distress, as other authors already highlighted (Steinweg et al., 2011; Marchesi et al., 2014; Montoro et al., 2016). In line with that, a significant relationship was found between DIF and anxiety, confirming the strong association between alexithymia and psychological distress in FMS. Moreover, pain experience and psychological distress had a significant relationship in the FMS group and this result is in line with previous research (Van Houdenhove and Luyten, 2006; Homann et al., 2012). In the light of these findings, we could hypothesize that in patients with FMS anxiety and depression affect both pain experience and emotional awareness and therefore they should be identified and taken into account in the treatment.

Strong correlations between alexithymia, pain and psychological distress were found in RD group. The positive correlation between difficulty in identifying feelings and the different components of pain was maintained, even after anxiety and depression was controlled. This finding suggests that in RD patients, alexithymia plays a more important role in influencing pain, regardless of the presence and severity of comorbid anxiety or depression.

With the aim of exploring the potential impact of alexithymia on the intensity and perception of pain, the clinical group (FMS + RD) was divided into patients with or without alexithymia, according to TAS-20 cut-off scores. Alexithymic patients (AL) had higher scores on anxiety, depression, pain intensity and perception than non-alexithymic ones (N-AL), according to previous studies (Makino et al., 2013; Saariaho et al., 2013; Di Tella et al., 2017). Two different regression models were obtained for AL vs. N-AL groups. In AL group, pain intensity was positively predicted by the sensory dimension of pain. In contrast with previous researches (Di Tella et al., 2017) our sample of patients experienced higher pain intensity that appeared not to be related with psychological distress and alexithymia, but only

TABLE 6 | Significant Pearson correlation coefficients *r*: associations between alexithymia, psychological distress and pain in patients with alexithymia (*n* = 40).

		1	2	3	4	5	6	7	8
1	DIF	–							
2	DDF	**0.381***	–						
3	EOT	**−0.318***	−0.046	–					
4	HADS-A	**0.366***	−0.108	−0.004	–				
5	HADS-D	0.064	**0.350***	0.089	**0.319***	–			
6	QUID-S	0.173	0.041	−0.230	0.152	0.237	–		
7	QUID-A	0.147	−0.084	−0.148	0.196	−0.051	**0.755****	–	
8	VAS	0.169	0.199	−0.136	0.267	0.247	**0.685****	**0.407****	–

*Same abbreviations as **Table 2**. Bold data indicate correlations that are significant. *p < 0.05; **p < 0.001.*

TABLE 7 | Significant Pearson correlation coefficients r: associations between alexithymia, psychological distress and pain in non-alexithymic patients (*n* = 34).

		1	2	3	4	5	6	7	8
1	DIF	–							
2	DDF	0.079	–						
3	EOT	−0.155	−0.170	–					
4	HADS-A	0.160	**−0.438****	**0.415***	–				
5	HADS-D	0.039	−0.318	**0.367***	**0.685*****	–			
6	QUID-S	**0.404***	−0.098	−0.031	0.172	0.003	–		
7	QUID-A	0.273	**−0.333***	0.093	0.295	0.212	**0.835*****	–	
8	VAS	0.319	−0.283	**0.340***	**0.668*****	**0.451****	0.323	**0.377***	–

*Same abbreviations as **Table 2**. Bold data indicate correlations that are significant. *p < 0.05; **p < 0.01; ***p < 0.001.*

with the sensory dimension of pain (periodic, pulsing, pounding, penetrating, burning, smarting, tender). Meanwhile, in this group, the relationship between psychological distress and alexithymia was confirmed, suggesting that alexithymia in chronic pain patients might be a state that arise from other psychological conditions (i.e., high levels of depression or anxiety). In the N-AL group instead, anxiety positively predicted pain intensity, confirming the association between psychological distress, alexithymia and pain whereas variables scores are subthreshold. These results were also confirmed in healthy subjects, where strong correlations between al clinical variables were found.

TABLE 8 | Results of multiple regression analysis predicting pain intensity (VAS) from DIF, EOT, HADS-A, HADS-D in alexithymic (*n* = 40) and non-alexithymic patients (*n* = 34).

Dependent variables	Predictors	β	S.E.	Lim. inf. (95%)	Lim. sup. (95%)	*P* values
Alexithymia						
VAS	Intercept	3.415	0.612	2.174	4.656	< **0.0001****
	QUID-S	12.636	2.557	7.455	17.816	< **0.0001****
	QUID-A	−2.532	1.756	−6.089	1.025	0.158
No alexithymia						
VAS	Intercept	−1.760	2.206	−6.280	2.759	0.432
	DIF	0.167	0.109	−0.057	0.390	0.137
	EOT	0.089	0.095	−0.105	0.283	0.357
	HADS_A	0.381	0.136	0.103	0.660	**0.009***
	HADS_D	−0.006	0.131	−0.274	0.262	0.965
	QUID-A	1.686	1.592	−1.575	4.948	0.299

*DIF, Difficulty Identifying Feelings; EOT, Externally-Oriented Thinking; HADS-A, Hamilton Anxiety and Depression Scale-Anxiety; HADS-D, Hamilton Anxiety and Depression Scale-Depression; β, unstandardized beta; S.E., standard error. Bold data indicate significant variables in regression model. *p < 0.01; **p < 0.001.*

Our results suggest that while clinical symptoms (pain intensity and experience, alexithymia, anxiety and depression) are increased in patients with fibromyalgia or RD, the relationship between pain and other variables disappeared. Two separated blocks of significant correlations appeared: on the one side, pain perception and pain experience are associated, on the other side alexithymia is related to negative affects states. This result also suggest that alexithymia may be a state phenomenon that arise from psychological distress and might be investigated with different scales or within longitudinal studies. Meanwhile, when symptoms of psychological distress and alexithymia were subthreshold, correlations with pain experience and intensity became stronger.

Limitations

The present study has some limitations that should be considered. The cross-sectional nature of the study does not allow inferences about the causal relations among the variables. Prospective studies could clarify the relation between alexithymia, pain and emotional distress and its trend over time. Moreover, the use of a self-report measure (TAS-20) to assess alexithymia may not have investigated this construct properly, since it requires subjects to identify and describing affects, which is compromised in alexithymic subjects. The future research could use clinical interviews to assess alexithymia. Moreover, the use of a small

sample did not permit the generalizability of the results to the fibromyalgia and arthritis patients population.

DATA AVAILABILITY

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Department of Surgical, Medical and Molecular Pathology, Critical and Care Medicine, University of Pisa. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC conceived the assessment. LM, FM, LB, and CC planned the assessment. LM, FM, and SL contributed to the healthy subjects' data acquisition. LM, FM, and SL contributed to the patients' data acquisition. MM and GO contributed to the data analysis. MM, GO, CC, and AG contributed to the data interpretation. LM, FM, GO, RC, PKH, and CC drafted the manuscript. All authors critically revised the manuscript and approved the final version to be published.

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Examining the Influence of Early Life Stress on Serum Lipid Profiles and Cognitive Functioning in Depressed Patients

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Background: Early childhood adversity is a strong predictor of the development of major depressive disorder (MDD), but not all depressed patients experience early life stress (ELS). Cardio-metabolic diseases and cognitive deficits often coincide in MDD and worsen its course and outcome. Adverse childhood experiences have been associated with elevated risk for cardiovascular disease (CVD), but little is known on the impact of ELS on cardiovascular risk factors in MDD. Here, we examined MDD patients with and without ELS to explore the effects of ELS on serum lipid and lipoprotein levels and on cognitive performances of the patients.

Methods: Participants with a mean age of 35 years (18–55 years) were recruited from the university mental health clinic and general community. Three groups, matched in age, gender and lifestyle were examined: MDD patients with ELS (n = 21), MDD patients without ELS (n = 21), and healthy controls (n = 20). The following CVD risk factors were assessed: serum lipids (total cholesterol, triglycerides, high- and low-density lipoproteins), body mass index and exercise in a typical week. MDD severity was measured by the Beck Depression Inventory. Childhood Trauma Questionnaire was used to assess early life adversities. Executive functions and attentional processes were assessed by the Wisconsin Card Sorting and Conners' Continuous Performance tests.

Results: Major depressive disorder patients with ELS had higher serum triglyceride and lower HDL-cholesterol concentrations compared to MDD patients without ELS. Linear regression analysis revealed that the severity of ELS had a significant negative association with HDL-cholesterol levels and significant positive associations with the serum levels of TG and TC/HDL-cholesterol index. We also found significant associations between some specific trauma types and lipid profiles. Finally, we could detect significant associations between depression severity and specific domains of the cognitive tests as well as between lipid profiles and certain domains of the Wisconsin Card Sorting Test. However, we could not detect any association between the severity of ELS and cognitive performance.

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Conclusion: After controlling for depressive symptom severity and lifestyle variables, ELS was found to be a strong predictor of serum lipid alterations. Several, inter-correlated pathways may mediate the undesirable effects of ELS on the course and outcome of MDD.

Keywords: adverse childhood experience, childhood adversity, cardiovascular risk, cholesterol, depression, HDL, major depressive disorder, triglyceride

INTRODUCTION

Major depressive disorder is a key public health concern today (Kessler, 2012), as it is a commonly occurring and an often recurring condition associated with considerable functional impairments, diminished quality of life, increased medical morbidity, and mortality (Kessler and Bromet, 2013). MDD often coincides with somatic illnesses such as metabolic syndrome (Pan et al., 2012) and CVD (Hare et al., 2014); nevertheless, the direction of the causal relationship between depression and cardio-metabolic diseases, as well as the specific underlying mechanisms, have not yet been fully understood. Moreover, patients suffering from MDD often present neurocognitive deficits (Austin et al., 2001; McDermott and Ebmeier, 2009; Lee et al., 2012; McIntyre et al., 2013; Rock et al., 2014).

Major depressive disorder is a clinically heterogeneous disorder, which is a result of manifold etiological factors, as well as developmental pathways. ELS, such as adverse childhood experiences (ACEs) (e.g., physical, emotional, and sexual abuse, neglect, parental loss, and poverty), have long been known to be strong predictors of MDD in adulthood (e.g., Widom et al., 2007; Norman et al., 2012; Lindert et al., 2014). A recent meta-analysis of 26 studies revealed that childhood emotional abuse and neglect showed the strongest association with depression risk in adults, while sexual/physical abuse or family violence have been proved to be non-specific risk factors for various mental disorders (Mandelli et al., 2015). Adult MDD with prior ELS is associated with earlier onset, more severe symptomatology, a greater number and longer duration of depressive episodes, a tendency to be chronic or therapy-resistant, higher rates of psychiatric comorbidities, as well as suicidal behavior or impulsivity compared to MDD without ELS (Brodsky et al., 2001; Zlotnick et al., 2001; Klein et al., 2009; Wiersma et al., 2009; Hovens et al., 2010; Miniati et al., 2010; Nanni et al., 2012). Moreover, ELS is also a risk factor for severe metabolic alterations and central obesity (Pervanidou and Chrousos, 2012; Davis et al., 2014) and CVD (Rich-Edwards et al., 2012; Loria et al., 2014). Furthermore, a recent study which analyzed data on cardio-metabolic markers of 9000 cohort members found that physical and sexual abuse was associated with high LDL-C and low serum levels of HDL-C, and that childhood neglect, as well as emotional abuse, was associated with raised TG and lower HDL-C (Li et al., 2019). In sum, ELS appears to be related to adult cardio-metabolic complications and comorbidities by two etiologic mechanisms: (1) the direct effect of early and late life stress; (2) general factors that are compensatory behaviors, as well as attempts at self-help by food and agents (Kesebir, 2014).

Serum lipid concentrations have been widely investigated in MDD, however, studies yielded inconsistent results. Both higher (Ledochowski et al., 2003; Nakao and Yano, 2004; Moreira et al., 2017) and lower serum TC levels (Olusi and Fido, 1996; Maes et al., 1997; Ong et al., 2016) were registered in patients with MDD compared to controls, and null findings have also been reported (Lehto et al., 2008; van Reedt Dortland et al., 2010; Enko et al., 2018). Alterations of serum concentrations of LDL-C were most widely studied in MDD. Recently, a comprehensive meta-analysis found significantly lower cross-sectional LDL-C serum concentrations in MDD compared to HCs, when LDL-C was modeled as a continuous measure (Persons and Fiedorowicz, 2016). The authors suggested a U-shaped relationship between depression severity and LDL-C. Nevertheless, this meta-analysis did not consider the effect of ELS on LDL-C concentration in depression. Studies that investigated the relationship between HDL-C and MDD had produced contradictory findings. Some studies found no association at all (Aijänseppä et al., 2002; Rice et al., 2010), while others revealed a correlation between lower HDL-C and depression (Kim et al., 2004; Ancelin et al., 2010) and one study reported higher HDL-C than matched controls (Olusi and Fido, 1996). Similarly, contradictory findings have been published in serum triglyceride levels in depressed patients. Kinder and co-workers reported on a positive correlation between triglyceride blood levels and depression in women aged between 17 and 39 years (Kinder et al., 2004), and a positive correlation between triglyceride blood levels and the BDI score was also found in women who had received coronary angiography (Vaccarino et al., 2008). But there are also negative findings demonstrating no difference in serum TG levels between control and depressed subjects (Pjrek et al., 2007). A number of theories have been put forward to explain the contradictory findings on serum lipid disturbances in depression. Most of them emphasize the influence of the methodology used for the clinical evaluation of depression (e.g., dimensional or categorical assessment), or the impact of demographic, lifestyle and clinical variables (van Reedt Dortland et al., 2010). Furthermore, some results imply that the inconsistent findings might be due to the heterogeneity of the illness and that the

Abbreviations: ACEs, adverse childhood experiences; BDI, Beck Depression Inventory; BMI, body mass index; CPT-II, Conner's Continuous Performance Test-II; CTQ EA, Childhood Trauma Questionnaire Emotional Abuse; CTQ EN, Childhood Trauma Questionnaire Emotional Neglect; CTQ PA, Childhood Trauma Questionnaire Physical Abuse; CTQ PN, Childhood Trauma Questionnaire Physical Neglect; CTQ SA, Childhood Trauma Questionnaire Sexual Abuse; CTQ, Childhood Trauma Questionnaire; CVD, cardiovascular disease; ELS, early life stress; HC, healthy control; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol; TG, triglycerides; WCST, Wisconsin Card Sorting Test.

lipid disturbances may be characteristic for only certain specific subgroups within the MDD.

So far, only a few studies considered the role of ELS in the association between depression and metabolic disturbances. McIntyre et al. (2012) found a significantly lower level of HDL-C in depressed patients who experienced childhood adversity, but there was no statistically significant difference in the overall rate of dyslipidemia and metabolic syndrome between subjects with and without childhood adversity. Ding et al. (2014) did a metabonomic analysis and reported that MDD patients had lower TC levels compared to controls, but patients with ELS had higher TC levels compared to the MDD only group. Wingenfeld et al. (2017) conducted a women-only study in a physically healthy clinical sample and found no difference in TG, cholesterol, HDL-C, LDL-C and other metabolic risk markers between MDD patients with and without sexual or physical abuse. However, one should carefully interpret these null findings, as the exclusion of obese individuals (with body mass index > 30 kg/m^2) might have led to an underrepresentation of subjects with existing obesity linked to ELS. More recently Deschênes et al. (2018) reported that ACEs are indirectly associated with diabetes via depressive symptoms and cardio-metabolic dysregulations. While Kraav et al. (2019) found decreased serum TC in depressed outpatients with a childhood history of physical violence. Importantly, most of these earlier studies – when they carried out the statistical analysis of their data – did not control for the effects of ELS, while it is well-known that the prevalence of ACEs is much higher in depressed patients compared to the general population, thus, the presence of ELS might be a confounding variable influencing the outcome of these investigations.

Psychodynamic factors, such as the loss of "good self" or "damaged self" might also have a significant impact. Individuals with ELS experience a defective or "wounded" self, and distressing feelings of shame originating from the internalization of bad or unworthy parents. According to the object relation theory, stressful life events can distort the mental representations of the self and others. This can significantly influence the individual's behavior, i.e., his or her affective states and self-care. Moreover, the damaged self can negatively impact health behavior and the adaptation to emerging somatic illnesses as well (Kohut, 1977; Ulman and Brothers, 1988; Marchini et al., 2018). Recent psychodynamic theories focus on the role of the attachment and attachment-based mentalizing capacities in the etiology and treatment of depressive disorders, and in the development of somatic disorders in individuals with ELS. Adopting a developmental approach, Luyten and Fonagy (2018) emphasized that ELS can lead to insecure attachment that impairs adaptation to stressful social situations and disrupts the regulation of the stress response. If social stress emerges, hypermentalizing and hypomentalizing can occur on the basis of the insecure attachment. These can lead to deficits of stress regulation, and to dysfunctional compensatory strategies (e.g., drug abuse, self-harm, sexual promiscuity, risk-taking, eating disorders). Due to the unhealthy behavior and the neurobiological changes as a result of ELS, MDD patients with ELS may suffer from stress-related cardiovascular and metabolic diseases more often.

In the present study, we hypothesized that serum lipid levels might be determined by ACEs in depressed patients, based on the following observations: (i) ELS can result in serum lipid alterations both in psychiatric (McIntyre et al., 2012; Misiak et al., 2015) and non-psychiatric samples (van Reedt Dortland et al., 2012; Spann et al., 2014); (ii) lipid disturbances were detected mostly in depressed patients with atypical or melancholic symptoms, or suicidal tendencies, which are more characteristic to depression with ELS (Harkness and Monroe, 2002; Matza et al., 2003; Klein et al., 2009). To investigate this hypothesis, we measured serum lipid and lipoprotein profiles in MDD patients with high and low ELS scores, and in age- and gender-matched HCs. Atherogenic indices (TC/HDL-C, LDL-C/HDL-C) and BMI was also calculated and we collected sociodemographic and clinical data on the participants' lifestyle as well. Finally, we used two well-established neuropsychological tests to measure the participant's executive functions (Wisconsin Card Sorting Test) and their attentional processes (Conners' Continuous Performance Test-II).

MATERIALS AND METHODS

Participants

Forty-two patients with MDD and 20 healthy controls (HCs) participated in this study. Patients with MDD were recruited from the Affective Disorder Unite of the Department of Psychiatry and Psychotherapy, University of Pécs, Hungary. The local Research Ethics Committee of the University of Pécs approved the study design and protocol (Ethical Approval Nr.: 2015/5626) and all participants provided written informed consent. To exclude the effects of aging, only subjects aged between 18 and 55 were involved in the study, because several studies reported an increased prevalence of dyslipidemia in the elderly population (Bechtold et al., 2006; Shanmugasundaram et al., 2010; Liu and Li, 2015).

All patients fulfilled the DSM-5 diagnostic criteria of MDD (American Psychiatric Association, 2013). Inclusion criteria of the MDD group included: (1) age 18–55 years; (2) a diagnosis of MDD in a current major depressive episode as assessed by a trained psychiatrist using the Structured Clinical Interview for DSM-5, Clinical Version, (SCID-5-CV) (First et al., 2015, 2016b) and the Structured Clinical Interview for DSM-5, Personality Disorders (SCID-5-PD) (First et al., 2016a, 2018). Exclusion criteria for the patient group were: current substance abuse or dependence (if the patient met diagnostic criteria, he or she had to be abstinent for at least 2 years), bipolar disorder, post-traumatic stress disorder, a history of any psychotic disorder, and current eating disorders. HC participants were recruited by online advertisements and via personal contacts of the researchers. The control sample was screened by a qualified psychiatrist to ascertain the absence of lifetime or family history of mental disorders. In addition, SCL-90 (Derogatis, 1977) was applied to rule out relevant subthreshold psychiatric symptoms in potentially healthy individuals. Exclusion criteria for both the patients and the controls were: liver or kidney disease, severe CVD, uncontrolled thyroid disorders, uncontrolled

diabetes mellitus, and current inflammatory illness. Subjects with known familial hyperlipidemia were not included. Subjects with neurological disorders, in addition, those with a history of head injury and with severe hearing or visual impairment, and an IQ < 85 were also excluded.

In the MDD group, treatment with antidepressant medication or psychotherapy were not exclusion criteria once the diagnosis had been established. Current psychotropic medication data were collected: 41 (97.6%) MDD subjects were taking antidepressants (20 patients were taking SSRIs, 12 mirtazapine, 2 mianserine, 2 venlafaxine, 1 duloxetine, 1 trazodone, 1 vortioxetine, 1 agomelatine), 21 (50%) low dose antipsychotics (17 quetiapine, 1 ziprasidone, 1 aripiprazole, 1 thiothixene), 5 (11.9%) mood stabilizing medications. None of the control subjects took psychotropic medication.

One MDD patient was on lipid-lowering drug (atorvastatin) treatment at the time of the study. Two patients and two control subjects kept a vegetarian diet.

Laboratory Analyses

Cubital venous blood was drawn from the participants between 7 and 8 AM in order to avoid any possible effect of circadian variations. The samples were collected following 8–12 h of fasting. Serum concentrations of TC, LDL-C, HDL-C, and TG were all measured with a Roche Modular (module P800) clinical chemistry analyzer, using enzymatic colorimetric test methods according to the manufacturer's instructions (Roche Diagnostics, Hungary).

Questionnaires

Beck Depression Inventory

The severity of actual depressive symptoms was assessed using the BDI (Beck et al., 1961; Hungarian adaptation: Petö et al., 1987; Rózsa et al., 1998). This is a 21-item self-report questionnaire rating the presence and extent of sadness, pessimism, past failure, loss of pleasure, self-dislike, self-criticism, and suicidal thoughts and wishes in the past week. The scores range from 0 to 63 points and higher scores indicate more severe depression. In this study, Cronbach's alfa values were excellent for the total BDI scores (0.95) and for the cognitive subscale scores (0.91), and good for the somatic-affective subscale (0.86).

Childhood Trauma Questionnaire-Short Form

Early life stress was surveyed with the 28-item retrospective self-report questionnaire of the Childhood Trauma Questionnaire-Short Form (CTQ) (Bernstein et al., 2003), that assesses the severity of five types of maltreatment before the age of 18 years: physical abuse (CTQ PA), emotional abuse (CTQ EA), physical neglect (CTQ PN), emotional neglect (CTQ EN), and sexual abuse (CTQ SA). Each subscale is measured with five 5-point scale items. The short form of the questionnaire is the most widely used version, which includes clinical cut-offs for significant abuse and neglect. Childhood maltreatment exposure was entered in the statistical analyses as a continuous variable with row scores, or it was coded into a two-level variable for dividing the MDD sample into low-ELS and high-ELS subgroups. Patients with MDD were assigned to the *MDD Only* subgroup if they had not experienced any types of moderate to severe childhood trauma. MDD patients were put into the *MDD + ELS* subgroup if they had at least one type of moderate to severe childhood trauma. In the present sample, the internal consistencies were excellent for the CTQ total score, and for the subscales of physical abuse, emotional abuse, sexual abuse, as well as for emotional neglect (Cronbach's alphas > 0.9). The internal consistency was acceptable for the subscale of physical neglect (Cronbach's alpha = 0.77). The Hungarian translation of the original (English) CTQ was done using the back-translation procedure (Sperber, 2004). Two senior authors (MS and BC) translated the English version to Hungarian. To ensure that the translated version is equivalent with the source version a bilingual linguist translated the early Hungarian version back to English. Errors of meaning and concept inconsistencies between the translated versions were discussed and corrected.

Sociodemographic Data on BMI and Lifestyle

A self-report questionnaire determined the various sociodemographic data, including education, lifestyle habits of regular exercise. Measurements for height and body mass were obtained using a wall-mounted stadiometer and electronic scale, respectively. BMI was calculated as body mass in kilograms divided by height in meters squared.

Neurocognitive Tests

Wisconsin Card Sorting Test

Executive functions were assessed by the computerized version of the WCST (Heaton, 1981). In the test, cards with geometric shapes (different in their number, color, and form) have to be matched according to varying sorting principles. The actual method of sorting has to be found out by the subject based on the provided feedback (correct or incorrect). Besides the number of total correct responses and non-perseverative errors, we detected the number of perseverative errors and conceptual level responses as a measure of shifting ability and conceptual ability, respectively. The WCST is a commonly used cognitive measure in clinical investigations including the studies examining cognitive changes related to depression (see e.g., Li et al., 2010; Giel et al., 2012; McGirr et al., 2012, etc.). Moreover, the WCST has been found to be a highly reliable test already decades ago (e.g., Tate et al., 1998).

Conner's Continuous Performance Test-II

Attentional processes were assessed by the CPT-II (Conners, 2000). In this task, respondents are required to press the space bar when any letter except X appears. The inter-stimulus intervals are variable (1, 2, or 4 s) with display time of 250 ms. There are six blocks, with three sub-blocks each containing 20 trials. The procedure takes 14 min to complete. Omission errors and commission errors, as well as hit reaction time and detectability (a measure of the difference between the signal [non-X] and noise [X] distributions), were assessed.

Conner's Continuous Performance Test-II is one of the most widely used, computer-administered cognitive test of attention and impulsivity. Since it is not a verbal test, and no language

adaptation is necessary thus, the reliability testing of this test was out of the scope of our study. A recent publication reported that CPT-II has a strong internal consistency, adequate test-retest reliability for commission errors and response time, and a relatively poor test-retest reliability for omission errors, and practice effects for omission and commission errors (Shaked et al., 2019). Moreover, CPT-II performances were unrelated to those in other cognitive tests, such as Stoop Color-Word test (Shaked et al., 2019). CPT-II is often used in clinical research on depression (see e.g., Godard et al., 2011; Parlar et al., 2016).

Since none of the clinical studies listed above (using either the CPT-II or the WCST) investigated the reliability of these cognitive tests, we followed the examples of the literature and assumed that both CPT-II and WCST were sufficiently reliable tests.

The Sequence of Data Collection

Research participants underwent the following study procedures. First, the clinical interviews and questionnaires were completed to assess the severity of depression and ELS. Then, a senior clinician blinded to the results of the CTQ data conducted a semi-structured interview about the stressful early life-events during childhood and adolescence. CTQ sores and the interview responses were compared, discrepancies were discussed with the participants. In the case of unresolvable discrepancies, participants were excluded from the study (n = 3). Cognitive functions were assessed separately the next day or the day after the next day. Blood samples were taken in the morning within 24 h after the initial clinical assessments.

Statistical Analysis

Statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS), version 21.0. Normality was checked by normal probability plots and by the Shapiro-Wilk and the Kolmogorov-Smirnov tests. Lipid and cognitive variables that showed skewed distributions were log-transformed, and all subsequent analyses were done with these transformed data. Between-group differences in demographic, lifestyle and clinical variables were analyzed by chi-square test and by ANOVA or non-parametric tests (Mann–Whitney U and Kruskal–Wallis). Differences between the study groups in the serum lipid and lipoprotein values, as well as cognitive performances, were tested first by one-way ANOVA. If the homogeneity assumption (tested by Levene's statistic) was violated, Welch-probe was used for the group comparisons. Fisher's LSD and Games-Howell tests were applied for *post hoc* pairwise comparisons. In the next step, between-group differences in the main variables were analyzed using ANCOVA with demographic and lifestyle variables as covariates and *post hoc* comparisons were done with Bonferroni correction.

After the group comparisons, hierarchical multiple linear regression analyses were run in the entire MDD group in order to explore whether the heterogeneity of lipid and lipoprotein levels were explained rather by the severity of depression or by the severity of ELS and whether there were associations between the revealed lipid alterations and the patients' cognitive performances. Due to the relatively large number of background variables and the relatively small sample size, in the regression analyses, we selected the most relevant confounders using the forward procedure, and predictor variables of main interest were added to the models with the enter method. In the forward procedure, the predictor variables were sequentially included in the regression models depending on the strength of their correlation with the criterion variable (P to enter < 0.05). The entering procedure enters the predictor variables in the models irrespective of their significance with the criterion. In all analyses, P-values (two-tailed) below 0.05 were considered statistically significant. Effect sizes were measured by calculating Cohen's d, η^2 (for ANOVAs) as well as Cohen's f^2 (for multiple regression analyses).

RESULTS

Demographic, Lifestyle, and Clinical Data

Two-Group Comparisons: Healthy Controls Versus the Entire MDD Group

There were no significant between-group differences in age ($F_{(1,60)}$ = 0.024, P = 0.877), gender ratio ($X^2_{(1)}$ = 1.303, P = 0.254), BMI (U = 398.000, Z = −0.331, P = 0.740), and regular physical activity (U = 345.500, Z = −1.167, P = 0.243). The level of education was significantly lower (U = 190.000, Z = −3.612, $P < 0.001$), while the BDI score, as well as all CTQ scores (including total score and trauma type sub-scores) were significantly higher in MDD patients compared to the healthy subjects (BDI: Welch's $F_{(1,47.7)} = 146.324$, $P < 0.001$); CTQ Total: U = 72.500, Z = −5.238, $P < 0.001$; CTQ PN: U = 110.000, Z = −4.787, $P < 0.001$; CTQ PA: U = 186,500, Z = −3.790, $P < 0.001$; CTQ EN: $F_{(1,60)}$ = 26.407, $P < 0.001$; CTQ EA: U = 116.500, Z = −4,585, $P < 0.001$; CTQ SA: U = 230.000, Z = −3.506, $P < 0.001$) (for details see **Table 1**).

Three-Group Comparisons: Healthy Controls Versus MDD Only Versus MDD + ELS

The three groups did not differ in age ($F_{(2,59)} = 0.125$, $P = 0.883$), gender ratio ($X^2_{(2)}$ = 1.428, P = 0.490), BMI ($X^2_{(2)}$ = 0.142, P = 0.931), and physical activity ($X^2_{(2)}$ = 3.083, P = 0.214), however, a significant difference could be observed between groups in years of education ($X^2_{(2)} = 14.079$, $P = 0.001$). Pairwise comparisons showed that the level of education was significantly lower in the MDD Only and in the MDD + ELS groups compared to HC (P = 0.025, P = 0.001, respectively). As expected, CTQ total score, and the specific trauma sub-scores were significantly different between groups (CTQ Total: $X^2_{(2)} = 46.768$, $P < 0.001$; CTQ PN: $X^2_{(2)}$ = 34.441, $P < 0.001$; CTQ PA: $X^2_{(2)}$ = 30.924, $P < 0.001$; CTQ EN: $F_{(2,59)}$ = 43.020, $P < 0.001$; CTQ EA: $X^2_{(2)}$ = 37.808, $P < 0.001$; CTQ SA: $X^2_{(2)}$ = 23.897, $P < 0.001$) and *post hoc* comparisons revealed that the MDD + ELS group had significantly higher scores in all CTQ scales than the MDD Only group (CTQ Total: $P <$ 001; CTQ PN: P = 0.002; CTQ PA: $P < 0.001$; CTQ EN: $P < 0.001$; CTQ EA: $P < 0.001$; CTQ SA: P = 0.002) (**Table 1**). The severity of ELS was significantly higher for physical and emotional neglect in the MDD Only group compared to HC (CTQ PN: P = 0.039; CTQ EN: P = 0.012),

TABLE 1 | Demographic, lifestyle and clinical characteristics of patients with MDD and HCs.

	HC (*n* = 20)	Entire MDD (*n* = 42)	MDD Only (*n* = 21)	MDD + ELS (*n* = 21)
Demographic and lifestyle characteristics				
Age (years)[a]	35.80 (8.53)	35.40 (9.73)	34.71 (8.17)	36.10 (11.24)
Gender (female/male)	13/7	33/9	17/4	16/5
Education (years)[b]	15.00 (5.00)	12.00 (1.00) ***	12.00 (2.00) §	12.00 (1.00) §§
Physical exercise per week (hours)	1–2	2–4	1–2	2–4
Body mass index (kg/m^2)[b]	23.39 (6.6)	23.11 (5.26)	23.12 (5.69)	23.11 (4.83)
Early life stress				
CTQ physical neglect[b]	5.00 (1.00)	9.00 (4.00) ***	7.00 (4.50) §	10.00 (5.50) §§§ $^{++}$
CTQ physical abuse[b]	5.00 (0.00)	7.00 (5.25) ***	5.00 (2.00)	10.00 (5.50) §§§ $^{+++}$
CTQ emotional neglect[a]	9.10 (3.51)	13.40 (5.42) ***	11.95 (3.56) §	18.95 (3.47) §§§ $^{+++}$
CTQ emotional abuse[b]	6.00 (2.75)	13.50 (10.25) ***	9.00 (5.50)	19.00 (5.00) §§§ $^{+++}$
CTQ sexual abuse[b]	5.00 (0.00)	5.00 (4.25) ***	5.00 (0.50)	9.00 (7.50) §§§ $^{++}$
CTQ total score[b]	29.00 (11.5)	54.50 (29.50) ***	40.00 (17.00)	69.00 (18.50) §§§ $^{+++}$
Clinical data				
BDI total score[a]	3.00 (2.13)	23.21 (10.38) ***	20.05 (10.29) §§§	26.38 (9.69) §§§
Age at the onset of MDD[b]	-	25.5 (17–32.25)	28 (18–34)	20 (16–31.5)
Number of lifetime depressive episodes[b]	-	2 (1.75–3)	2 (1–3)	2 (2–3)
Double depression (*n*)	-	2	1	1
Chronic depression (*n*)	-	5	1	4
Recurrent depression (*n*)	-	31	13	18
Lipid profile				
Total cholesterol (mmol/L)[a]	4.85 (0.91)	5.10 (1.08)	5.04 (0.88)	5.16 (1.27)
Triglycerides (mmol/L)[b]	0.89 (0.93)	1.06 (0.78)	0.92 (0.39)	1.26 (1.05) $^{+}$
HDL cholesterol (mmol/L)[a]	1.65 (0.33)	1.58 (0.37)	1.70 (0.40)	1.45 (0.28) $^{+}$
LDL cholesterol (mmol/L)[a]	2.73 (0.77)	2.95 (0.79)	2.87 (0.61)	3.03 (0.95)
LDL-C/HDL-C[b]	1.75 (0.78)	1.81 (1.05)	1.70 (0.69)	2.00 (1.33)
TC/HDL-C[b]	3.04 (1.13)	3.22 (1.29)	3.04 (1.03)	3.27 (1.78) § $^{+}$

[a]*Means and standard deviations are presented.* [b]*Medians and inter-quartile ranges are presented. Two-group comparisons: overall MDD group compared to HC: *P < 0.05, **P < 0.01, ***P < 0.001. Three-group comparisons: MDD Only compared to MDD + ELS: $^{+}$P < 0.05, $^{++}$P < 0.01, $^{+++}$P < 0.001. MDD Only or MDD + ELS compared to HC: § P < 0.05, §§ P < 0.01, §§§ P < 0.001. BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire-Short Form; ELS, early life stress; HC, healthy controls; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.*

but there was no significant difference in CTQ total score, as well as in physical, emotional, and sexual abuse between these two groups (CTQ Total: $P = 0.051$; CTQ PA: $P = 0.596$; CTQ EA: $P = 0.149$; CTQ SA: $P = 0.515$). There was significant difference between the groups in BDI score (Welch's $F_{(2.29,0)} = 80.404$, $P < 0.001$) and the pairwise comparisons demonstrated that both MDD subgroups had significantly higher BDI score than the HC group ($P < 0.001$), whereas depression severity was similar in the two MDD subgroups ($P = 0.113$) (**Table 1**).

Lipid Profile

Two-Group Comparisons: Healthy Controls Versus the Entire MDD Group

No difference was found between the two groups by one-way ANOVA when we compared serum TC ($F_{(1,60)} = 0.782$, $P = 0.380$), TG ($F_{(1,60)} = 0.426$, $P = 0.516$), HDL-C ($F_{(1,60)} = 0.609$, $P = 0.438$), LDL-C ($F_{(1,60)} = 1.062$, $P = 0.307$), and the two atherogenic indices (LDL-C/HDL-C: $F_{(1,60)} = 2.052$, $P = 0.157$, TC/HDL-C: $F_{(1,60)} = 2.036$, $P = 0.159$) (**Table 1**). In order to control for the effects of demographic and lifestyle variables on lipid and lipoprotein levels, ANCOVAs were conducted with age, gender, level of education, physical exercise, and BMI as covariates, but again no significances were found (**Figure 1** and **Supplementary Table 1**).

Three-Group Comparisons: Healthy Controls Versus MDD Only Versus MDD + ELS

Results of the ANOVA omnibus tests indicated significant between-group differences in TG (Welch's $F_{(2,35.4)} = 4.367$, $P = 0.020$), HDL-C ($F_{(2,59)} = 3.293$, $P = 0.044$), and TC/HDL-C ($F_{(2,59)} = 3.434$, $P = 0.039$). *Post hoc* comparisons (Fisher's LSD and Games-Howell tests) showed that the level of HDL-C was significantly lower ($P = 0.018$), while the level of TG ($P = 0.015$) and also the ratio TC/HDL-C ($p = 0.034$) were significantly higher in the MDD + ELS than in the MDD Only group. The ratio of TC/HDL-C of the MDD + ELS group was also significantly higher when compared to the HC group ($P = 0.022$) There were no significant differences between groups in TC (Welch's $F_{(2,38.7)} = 4.367$, $P = 0.645$), LDL-C ($F_{(2,59)} = 0.733$, $P = 0.485$), and LDL-C/HDL-C ($F_{(2,59)} = 2.562$, $P = 0.086$) (**Table 1**). Cohen's *d*-values for all significant group differences ranged from 0.68 to 0.78 indicating medium-to-large effect sizes.

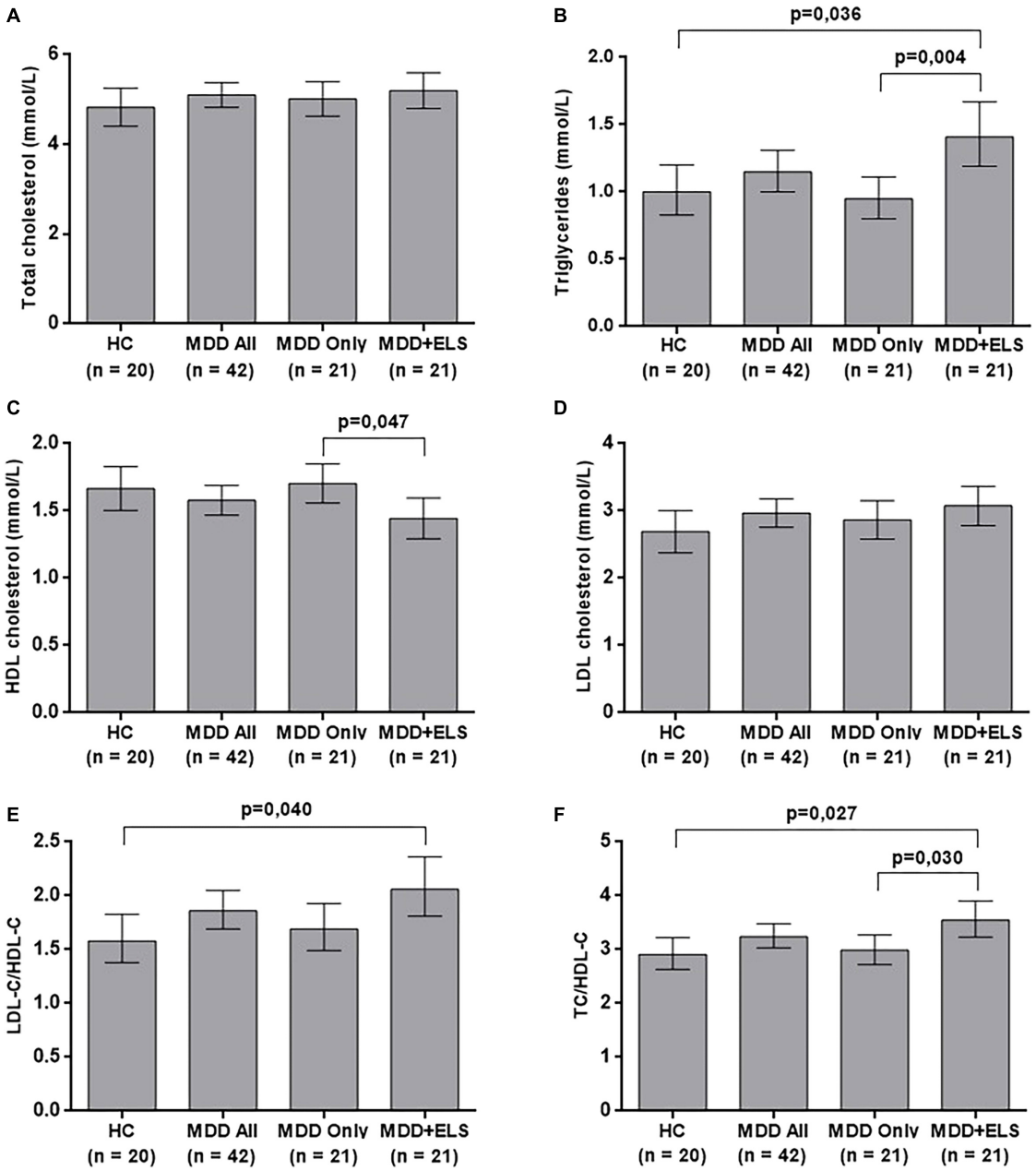

FIGURE 1 | Serum lipid and lipoprotein levels in HCs and depressed patients after the adjustment for age, gender, education, physical exercise per week, and body mass index. **(A)** total cholesterol levels; **(B)** triglyceride levels; **(C)** high-density lipoprotein cholesterol levels; **(D)** low-density lipoprotein cholesterol levels; **(E)** LDL-C/HDL-C ratio; **(F)** TC/HDL-C ratio. The bars represent the means and upper and lower 95% confidence intervals of the examined lipid profile elements. The values of triglycerides, LDL-C/HDL-C and TC/HDL-C are results of back-transformation (antilog) because of the skewed distribution of the original data. The *P*-values of significant differences are shown. ELS, early life stress; HC, healthy controls; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol.

After controlling for the effects of age, gender, level of education, physical exercise and BMI by ANCOVA, between-group differences remained significant in TG ($F_{(2,54)}$ = 6.320, P = 0.003), HDL-C ($F_{(2,54)}$ = 3.409, P = 0.040), and TC/HDL-C ($F_{(2,54)}$ = 4.854, P = 0.012), and a new significant difference emerged in LDL-C/HDL-C ($F_{(2,54)}$ = 3.794, P = 0.029). As it is shown in **Figure 1**, *post hoc* Bonferroni comparisons demonstrated that HDL-C was significantly lower in MDD patients with ELS than in MDD Only patients, as well as the TG and the TC/HDL-C index, were significantly higher in the MDD + ELS group compared both to the MDD Only and to the HC groups. Moreover, higher LDL-C/HDL-C ratio was revealed in MDD + ELS patients relative to the HC. There were no significant differences between groups by ANCOVA in TC

($F_{(2,54)} = 0.742$, $P = 0.481$) and LDL-C ($F_{(2,54)} = 1.454$, $P = 0.243$) (**Figure 1**). For the significant group comparisons, Cohen's *d*-values ranged from 0.63 to 0.94 (medium-to-large effect sizes).

Multiple Linear Regression Analyses: The Effects of Depression Severity and ELS on Serum Lipid/Lipoprotein Levels

Next, we performed a series of hierarchical linear regression analyses in the entire MDD group to determine whether the heterogeneity of each lipid/lipoprotein level is explained by the severity of depression or by the amount of ELS after controlling for each other and for potentially confounding factors. Relevant confounders were selected from the demographic variables (age, gender, years of education) in Block 1, and from the lifestyle variables (BMI, physical exercise per week) in Block 2 using the forward variable selection procedure. Because we were interested in how the statistical effect of current depression severity on lipid/lipoprotein levels changes after including ELS in the models, next, in Block 3, depression severity (BDI score), and finally, in Block 4, the amount of ELS (CTQ total score) were added to the regression models using the enter method.

After running hierarchical regression analyses for each lipid and lipoprotein parameters as dependent variables, we found that in Block 3, BDI score predicted only HDL-C ($P = 0.010$) significantly. However, when the CTQ total score was also added in Block 4, the relationship between BDI and HDL-C lost its significance ($P = 0.068$) and no other significantly predictive relationship emerged between depression severity and any of the lipid profile elements (**Table 2**). However, in Block 4, the severity of ELS had a significant negative association with HDL-C level ($P = 0.040$) and a significant positive association with the serum level of TG ($P = 0.014$) and TC/HDL-C index ($P = 0.043$) (for details see **Supplementary Table 2**). Cohen's f^2-values for these significant associations ranged from 0.11 to 0.18 indicating moderate effect sizes.

The Relationship Between the Different Subtypes of ELS and Serum Lipid/Lipoprotein Levels

Within the entire MDD group, additional series of hierarchical linear regressions were calculated to determine which subtypes of childhood adversities can significantly predict the parameters of the lipid profile as dependent variables after controlling for demographic variables (Block 1), lifestyle variables (Block 2), and depression severity (BDI score; Block 3) with the forward variable selection method. In Block 4, the CTQ subscores of the different trauma types, as predictor variables of main interest, were added to the models using the 'enter' procedure.

As it is shown in **Table 3**, we found significant negative associations between physical neglect and abuse and between HDL-C. We also found significant positive associations between physical and emotional neglect and abuse, and the levels of TG. Moreover, significant positive associations were found between physical and emotional neglect and the indices of LDL-C/HDL-C and TC/HDL-C. Sexual abuse had no statistically significant relationship between any of the lipid parameters (**Table 3**; for details see **Supplementary Table 3**).

Neurocognitive Tests

Two-Group Comparisons: Healthy Controls Versus the Entire MDD Group

One-way ANOVA revealed significant group differences when we compared omission errors of the Conner's Continuous Performance Test (Welch's $F_{(1,58.5)} = 7.464$, $P = 0.008$, Cohen's $d = 0.75$). Similarly, one-way ANOVA revealed significant group differences when we compared perseverative errors of the WCST (Welch's $F_{(1,50.8)} = 5.463$, $P = 0.023$, Cohen's $d = 0.63$) (for details see **Supplementary Table 4**). After controlling by ANCOVA for age, gender, and level of education, however, these differences lost their significance (**Supplementary Table 5**).

Three-Group Comparisons: Healthy Controls Versus MDD Only Versus MDD + ELS

The ANOVA omnibus tests revealed that omission errors of the Conner's Continuous Performance Test were significantly different in the three groups (Welch's $F_{(2,36.6)} = 3.780$, $P = 0.032$, Cohen's $d = 0.64$). Further comparison with the Games-Howell *post hoc* test revealed that the CPT omission errors were significantly higher in the MDD + ELS group than in the HC ($P = 0.045$, Cohen's $d = 0.65$) (for details see **Supplementary Table 4**). However, after controlling for the effects of demographic variables, no significant between-group differences were found in the neurocognitive variables (**Supplementary Table 5**).

The Effect of Serum Lipid/Lipoprotein Levels on Neurocognitive Performances in MDD

Finally, hierarchical multiple linear regressions were calculated to predict parameters of neurocognitive tests based on lipid parameters after controlling for demographic variables (Block 1), lifestyle variables (Block 2), severity of depression (i.e., BDI score; Block 3), and severity of ELS (i.e., CTQ total score; Block 4) that were included in the regression models with the forward procedure. The lipid profile elements, as predictor variables of main interest, were added to the models using the enter method in Block 5.

Depression severity predicted commission errors in the Conner's Continuous Performance Test ($\beta = 0.289$, $P = 0.024$) and detectability ($\beta = -0.304$, $P = 0.020$), as well as conceptual level responses in the WCST ($\beta = -0{,}416$, $P = 0.006$) in Block 3 (for details see **Supplementary Tables 6**, **7**). For these significant associations between depression severity and cognitive performances, Cohen's f^2-values ranged from 0.15 to 0.20 suggesting moderate effect sizes. However, we could not find any association between the amount of ELS and any of the neurocognitive test results in Block 4. No relationship was found between lipid parameters and any of the Conner's Continuous Performance Test results (**Supplementary Table 6**). However, we could detect significant negative associations between the lipid profiles and between specific domains of the WCST. There were significant negative associations between HDL-C and WCST perseverative errors, between LDL-C/HDL-C ratio and WCST total correct responses, and also between the indices LDL-C/HDL-C and TC/HDL-C, and WCST conceptual level responses (**Table 4**, for details, see **Supplementary Table 7**).

Cohen's f^2-values for these results ranged from 0.10 to 0.16 suggesting moderate effect sizes.

DISCUSSION

The principal aim of the present study was to examine the impact of childhood adversities on serum lipid profiles in depressed patients. In our statistical analysis, we asked the question of whether depression severity or the severity of ACEs have a stronger influence determining serum lipid levels. Overall, ELS was a stronger predictor of serum lipid profiles than depression severity. Furthermore, we found that depressed patients with ELS had significantly higher serum triglyceride and lower HDL-cholesterol concentrations compared to MDD patients without ELS. The atherogenic indices, LDL-C/HDL-C, and TC/HDL-C were also higher in patients with ELS. We also found significant associations between the different trauma types and lipid profiles.

TABLE 2 | Hierarchical linear regression analyses predicting serum lipid and lipoprotein levels in the entire MDD group.

Dependent variable	Blocks	Predictors	R^2	ΔR^2	β	β'
Total cholesterol	Block 1 (forward)	Age	0.157	0.157	0.396**	0.381**
	Block 2 (forward)	Body mass index	0.304	0.147	0.384**	0.382**
	Block 3 (enter)	**Depression severity**	0.311	0.007	−0.084	−0.080
	Block 4 (enter)	**Early life stress**	0.312	0.000		−0.013
Triglycerides	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.108	0.108	−0.328*	−0.396*
	Block 3 (enter)	**Depression severity**	0.145	0.038	0.198	0.031
	Block 4 (enter)	**Early life stress**	0.273	0.128		**0.400***
HDL cholesterol	Block 1 (forward)	No variable associated				
	Block 2 (forward)	No variable associated				
	Block 3 (enter)	**Depression severity**	0.156	0.156	**−0.395***	−0.280†
	Block 4 (enter)	**Early life stress**	0.243	0.088		**−0.317***
LDL cholesterol	Block 1 (forward)	Age	0.151	0.151	0.388*	0.392**
	Block 2 (forward)	Physical exercise	0.318	0.167	−0.409**	−0.453**
	Block 3 (enter)	**Depression severity**	0.327	0.009	−0.096	−0.134
	Block 4 (enter)	**Early life stress**	0.333	0.007		0.092
LDL-C/HDL-C	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.129	0.129	−0.359*	−0.391*
	Block 3 (enter)	**Depression severity**	0.177	0.048	0.223	0.104
	Block 4 (enter)	**Early life stress**	0.242	0.065		0.286†
TC/HDL-C	Block 1 (forward)	No variable associated				
	Block 2 (forward)	Physical exercise	0.126	0.126	−0.355*	−0.394*
	Block 3 (enter)	**Depression severity**	0.181	0.055	0.240	0.104
	Block 4 (enter)	**Early life stress**	0.266	0.085		**0.326***

*Input variables: Block 1: demographic variables (age, gender, and years of education); Block 2: lifestyle variables (body mass index and physical exercise per week); Block 3: depression severity (BDI score); Block 4: early life stress (CTQ total score). †P < 0.1,*P < 0.05, **P < 0.01. β, standardized beta coefficient at the current step; β', the standardized beta coefficient in the final model; BDI, Beck Depression Inventory; CTQ, Childhood Trauma Questionnaire-Short Form; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD; major depressive disorder; TC, total cholesterol. Bold values indicate the significant differences related to depression severity and ELS.*

TABLE 3 | Linear regression analyses with serum lipid and lipoprotein levels as dependent variables, and with trauma types (CTQ sub-scores) as predictors in the entire MDD group.

	Total cholesterol[a]		Triglycerides[b]		HDL cholesterol[c]		LDL cholesterol[d]		LDL-C/HDL-C[b]		TC/HDL-C[b]	
	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*	β	*p*
CTQ physical neglect	0.150	0.277	**0.351**	**0.017**	**−0.306**	**0.034**	0.179	0.182	**0.392**	**0.006**	**0.403**	**0.005**
CTQ physical abuse	−0.166	0.231	**0.320**	**0.031**	**−0.304**	**0.037**	−0.089	0.516	0.200	0.180	0.197	0.187
CTQ emotional neglect	0.176	0.198	**0.381**	**0.010**	−0.200	0.188	0.194	0.148	**0.358**	**0.014**	**0.419**	**0.004**
CTQ emotional abuse	−0.087	0.529	**0.308**	**0.041**	−0.291	0.054	0.008	0.956	0.223	0.138	0.248	0.099
CTQ sexual abuse	−0.240	0.083	0.114	0.463	0.050	0.764	−0.195	0.169	0.003	0.984	0.045	0.772

[a]Adjusted for age and body mass index. [b]Adjusted for physical exercise per week. [c]Adjusted for depression severity. [d]Adjusted for age and physical exercise per week. CTQ, Childhood Trauma Questionnaire Short Form; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD, major depressive disorder; TC, total cholesterol. Bold values indicate the significant differences.

TABLE 4 | Linear regression analyses of serum lipid and lipoprotein levels as predictors of executive functioning (WCST scores) in the entire MDD group.

	WCST total correct responses		WCST perseverative errors[a]		WCST non-perseverative errors[b]		WCST conceptual level responses[c]	
	β	*p*	β	*p*	β	*p*	β	*p*
Total cholesterol	−0.130	0.411	−0.088	0.532	−0.038	0.794	−0.153	0.292
Triglycerides	−0.235	0.134	0.219	0.100	0.062	0.673	−0.266	0.074
HDL cholesterol	0.167	0.290	**−0.283**	**0.027**	−0.167	0.255	0.192	0.224
LDL cholesterol	−0.236	0.133	−0.068	0.629	−0.036	0.806	−0.241	0.093
LDL-C/HDL-C	**−0.306**	**0.048**	0.151	0.251	0.105	0.471	**−0.340**	**0.022**
TC/HDL-C	−0.252	0.108	0.193	0.139	0.146	0.318	**−0.309**	**0.039**

[a]Adjusted for age and education. [b]Adjusted for education. [c]Adjusted for depression severity. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MDD; major depressive disorder; TC, total cholesterol; WCST, Wisconsin Card Sorting Test. Bold values indicate the significant differences.

Both physical and emotional neglect and abuse had a significant positive association with serum triglyceride levels, while physical neglect and abuse had a significant negative association with HDL-cholesterol. Finally, we could detect significant associations between depression severity and specific domains of the cognitive tests as well as between lipid profiles and certain results of the WCST. But in our study, ELS had no influence on the cognitive performance of the subjects.

A vast number of studies report that early life adversity may increase cardiovascular risk factors and the occurrence of CVD (Batten et al., 2004; Dong et al., 2004; Goodwin and Stein, 2004; Danese et al., 2009; Fuller-Thomson et al., 2010, 2012; Korkeila et al., 2010; Stein et al., 2010; Scott et al., 2011; Rich-Edwards et al., 2012; Basu et al., 2017; Murphy et al., 2017; Reid et al., 2018; Doom et al., 2019; Obi et al., 2019). These studies document that childhood adversities are associated with hypertension (Danese et al., 2009; Stein et al., 2010; Reid et al., 2018; Doom et al., 2019), higher BMI (Doom et al., 2019), ischemic heart disease (Dong et al., 2004) and myocardial infarction (Fuller-Thomson et al., 2012). Adverse childhood experience may alter serum lipid/lipoprotein profiles as adults with ELS may have elevated serum TG, LDL-cholesterol and TC as well as low HDL-cholesterol (Danese et al., 2009; Spann et al., 2014; Reid et al., 2018; Doom et al., 2019). Furthermore, a recent study reported that the different trauma types can be associated with specific changes in serum levels, i.e., physical and sexual abuse were associated with high LDL-C and low HDL-C, and childhood neglect with raised TG and low HDL-C (Li et al., 2019). The exact physiological pathways connecting ELS with CVD risk factors and CVD are yet unknown. Recently, a hypothesis has been put forward that experiencing social threat and adversity up-regulates pro-inflammatory cytokines which in turn may elicit depressive symptoms as well as metabolic syndrome and CVD (Slavich and Irwin, 2014).

Large body of evidence indicate that there is a strong association between MDD and CVD (Musselman et al., 1998; Penninx et al., 2001; Carney et al., 2002; Barth et al., 2004; Whooley, 2006; Van der Kooy et al., 2007; Goldstein et al., 2015). While the exact relationship between these two disorders remains obscure there is evidence that the presence of depressive symptoms can increase the risk of CVD (Joynt et al., 2003; Almeida et al., 2007; Vancampfort et al., 2014; Pérez-Piñar et al., 2016). Among the various CVD risk factors dyslipidemia has also been associated with depressed mood (Huang et al., 2003; Papakostas et al., 2004; van Reedt Dortland et al., 2010, 2013; Chien et al., 2013). However, the studies investigating serum lipid concentrations in MDD yielded inconsistent results. There are reports on higher (Ledochowski et al., 2003; Nakao and Yano, 2004; Moreira et al., 2017) as well as lower serum TC levels (Olusi and Fido, 1996; Maes et al., 1997; Ong et al., 2016) compared to controls, while others found no difference (Lehto et al., 2008; van Reedt Dortland et al., 2010; Enko et al., 2018). Other studies found that TG levels are increased in patients with MDD and that TG levels show a positive relationship with depression severity (Sevincok et al., 2001; Huang and Chen, 2004; Liu et al., 2016).

So far only a handful of studies examined the influence of childhood adversity on lipid profiles in depressed patients. McIntyre et al. (2012) examined a clinical population with unipolar depression and found a significantly lower level of HDL-C in patients who experienced traumatic life events during their childhood compared to those without childhood adversities. However, there was no statistically significant difference in the overall rate of dyslipidemia and/or metabolic syndrome between subjects with and without childhood adversity. Wingenfeld et al. (2017) conducted a women-only study in a physically healthy clinical sample and detected no difference in TG, cholesterol, HDL-C, LDL-C and other metabolic risk markers between MDD patients with and without sexual or physical abuse. More recently Deschênes et al. (2018) reported that ACEs are indirectly associated with diabetes via depressive symptoms and cardio-metabolic dysregulations. The most recent study found decreased TC levels in adult outpatients with MDD with a childhood history of physical violence (Kraav et al., 2019). The same study found no differences in serum levels of HDL-C and LDL-C between the groups (Kraav et al., 2019). In our present study, we could detect higher serum triglyceride and lower HDL-cholesterol levels in MDD patients who experienced childhood adversity compared to MDD patients without ELS. Furthermore, we also found that the severity of ELS had a negative association with HDL-cholesterol levels and positive associations with the serum level of TG and TC/HDL-C index. Thus, our present data support the notion that childhood adversity may influence serum lipid levels also in depressed individuals and that MDD patients with a history of childhood adversity may represent a specific sub-group within MDD. We could also detect significant associations between the different trauma types and lipid profiles. Physical neglect and

abuse had a significant negative association with HDL-cholesterol while physical and emotional neglect and abuse had a significant positive association with serum triglyceride levels. Our findings are in harmony with the recent report of Li et al. (2019), which reported that physical abuse was associated with low HDL-C, while neglect was associated with raised TG and lower HDL-C. In our present study, we could not detect any association between sexual abuse and serum lipid/lipoprotein levels. Others found that sexual abuse was associated with high LDL-C and low HDL-C (Li et al., 2019). There is, in fact, ample evidence in the literature that childhood sexual abuse can increase the incidence of CVD: a US study involving 5 900 subjects reported that childhood sexual abuse was associated with increased risk of cardiac disease (Goodwin and Stein, 2004). Another US survey involving 12 900 individuals found that specifically in men childhood sexual abuse was associated with heart attack (Fuller-Thomson et al., 2012). One should add that there are negative findings as well, e.g., a recent retrospective study involving 3 600 individuals could not reveal any consistent association between the specific type of early psychosocial adversity and CVD risk factors (Anderson et al., 2018). This study examined associations of specific types of psychosocial adversities, such as lack of maternal care, maternal overprotection, parental mental illness, household dysfunction, sexual abuse, physical and emotional abuse, and neglect in childhood with CVD risk factors including BMI, TG, low and high density lipoprotein cholesterol (Anderson et al., 2018).

A vast body of work has linked early life adversity to various types of cognitive deficits later in life (see e.g., Evans and Schamberg, 2009; Mueller et al., 2010; Pechtel and Pizzagalli, 2011; Gould et al., 2012; Chen and Baram, 2016). Cognitive impairments are also frequently present in depressed individuals (Porter et al., 2003; Marazziti et al., 2010; Ahern and Semkovska, 2017). A meta-analysis found significant cognitive deficits in executive function, memory and attention in depressed patients relative to controls (Rock et al., 2014), yet another one revealed significant correlations between depression severity and specific domains of episodic memory, executive function, and processing speed (McDermott and Ebmeier, 2009). In our present study, we could also detect significant associations between depression severity and specific domains of attention (examined with the CPT-II) and executive functions (investigated with the WCST). However, we could not find any association between ELS and cognitive performance using these two tests.

Numerous clinical and preclinical data suggest that dyslipidemia can be linked to cognitive deficits and decline (Yaffe et al., 2002; Farr et al., 2008; Gendle et al., 2008; Morley and Banks, 2010; Reynolds et al., 2010) though this issue is not without controversies (see e.g., Panza et al., 2006; Anstey et al., 2008). For example, there are reports that high TG are associated with poor memory and general cognitive decline (de Frias et al., 2007; Morley and Banks, 2010), and that high triglyceride levels inversely correlate with executive function in non-demented elderly adults (Parthasarathy et al., 2017). Furthermore, a recent study documented elevated triglyceride levels in patients with MDD, which was associated with cognitive impairments (Shao et al., 2017). In our study, we found negative associations between lipid profiles (HDL-C and LDL-C/HDL-C, TC/HDL-C ratios) and specific domains of the WCST measuring executive functions. Low levels of HDL cholesterol have been associated with poor memory (Singh-Manoux et al., 2008; Feinkohl et al., 2019), impaired executive functions (Sun et al., 2019) and cognitive decline (van Exel et al., 2002), as well as with lower gray matter volumes (Ward et al., 2010). It should be added here that higher levels of HDL-C have been associated with a decreased risk of Alzheimer's disease (Reitz et al., 2010) and that low HDL-C levels can result in cerebral amyloidosis (Reed et al., 2014).

The low sample size is a major limitation of this study. A further important limitation is that we used a retrospective self-report to asses ELS. Ideally, the long-term effects of childhood adversities should be studied in prospective longitudinal studies and using qualitative or mixed methods can also add further valuable information when studying the impact of experienced traumas (see e.g., Boeije et al., 2013; Esposito et al., 2019), especially because self-reports can be biased. For example, social desirability can be an important potential bias when reporting past traumatic events especially in health-related research (see e.g., Adams et al., 2005; van de Mortel, 2008; Caputo, 2017 on this topic). Another limitation of our study design is that it does not allow to derive causal relations, but only associations. To compensate these limitations we did our best to carefully select the participants and match them in age, gender, lifestyle habits, and clinical data. Notably, only a few studies (Ding et al., 2014; Wingenfeld et al., 2017) included a control group in their studies, besides the MDD patients with or without ELS. We also carefully analyzed the influence of the various ACE subtypes. Finally, we also assessed the cognitive performance of our subjects and none of the earlier studies did such measurements.

Our present findings, together with the results available in the literature, have important clinical implications regarding the psychological interventions in case of depressed patients with ELS. Several studies demonstrated that depressed adults who experienced ELS react less well to conventional treatments than those who were not exposed to stressful life events during childhood (reviewed by Targum and Nemeroff, 2019). There is some evidence that MDD with ELS reacts much better to cognitive behavioral therapy (Nemeroff et al., 2003; Niciu et al., 2015) or interpersonal therapy (Zobel et al., 2011) than to pharmacotherapy. Psychodynamic therapies, as well as mentalizing-based therapy, can also be beneficial for MDD patients with ELS (Alessi and Kahn, 2017; Luyten and Fonagy, 2018). Our data emphasize the importance of the screening for ELS in the clinical MDD population. In case of early emotional abuse and emotional and physical neglect, we should consider psychotherapeutic interventions. Relying on relational cooperation, psychodynamic psychotherapy interventions can be especially helpful for patients with ELS, as they can establish an atmosphere of acceptance and safety, factors that are extremely relevant in early traumatized individuals. The holding environment and containment, created in this way, can provide a basis for the therapy of mood symptoms, and it may also reduce the risks for somatic complications. In addition, mentalizing based therapy can support early traumatized patients with an insecure attachment to regulate their negative affective states, and

reduce stress, instead of using unhealthy methods to cope with stressful situations.

In summary, our present data provide further evidence that childhood adversity may increase the risk of CVD. We found that depressed patients with ELS had higher serum triglyceride and lower HDL-cholesterol concentrations compared to patients without ELS. The severity of childhood adversity and the different trauma types showed specific associations with the lipid profiles, but we could not find any association between the severity of ELS and cognitive performance. Further research is needed to clarify the exact intermediary factors in order to gain a better understanding on the physiological mechanisms linking childhood adversities to cardio-metabolic disease, including the exploration of the difference as well as common pathways for specific maltreatment. Importantly, these issues should preferably be investigated in longitudinal studies as the retrospective self-reported measures might be biased. Finally, our present findings highlight the importance of controlling ELS, especially when a psychiatric sample is studied and treated.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

ETHICS STATEMENT

The local Research Ethics Committee of the University of Pécs approved the study design and protocol (Ethical Approval Nr.: 2015/5626) and all participants provided written informed consent.

AUTHOR CONTRIBUTIONS

ÁP, BC, and MS conceived the study, designed the experiments, and wrote the manuscript. NN carried out the psychological and neurocognitive tests with the subjects, analyzed the data, prepared the tables and the figure, and wrote the manuscript. RH helped with the statistical analysis. MS selected the patients and made the diagnosis. TT and AM provided supervision and had helpful comments on the interpretation of the data. All authors contributed to the writing of the manuscript and/or revising it critically for important intellectual content, approved the final version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.01798/full#supplementary-material

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BRIEF RESEARCH REPORT
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Effects of Metabolic Syndrome on Cognitive Performance of Adults During Exercise

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The metabolic syndrome (MS) has been associated with poor performances in multiple cognitive domains, as processing speed, visuo-spatial abilities, and executive functioning. Exercise is a critical factor for MS people's vulnerability to cognitive dysfunction, because this may be beneficial to reduce cognitive impairment, but limited physical activity and impaired cerebral blood flow in response to exercise have been reported by individuals suffering from MS. Using an attentional interference test, the Bivalent Shape Task (BST), and metaboreflex, we analyzed cognitive performance and cerebral oxygenation (COX) in 13 MS people (five women), and 14 normal age-matched control (CTL, six women). Five different sessions were administered to all participants, each lasting 12 min: control exercise recovery (CER), post-exercise muscle ischemia (PEMI) to activate the metaboreflex, CER + BST, PEMI + BST, and BST alone. During each session, cognitive performance was assessed by means of response times and response accuracy with which participants make the decision and COX was evaluated by near infrared spectroscopy with sensors applied in the forehead. Compared to CTL, MS group performed significantly worse in all sessions ($F = 4.18$; $p = 0.05$; ES = 0.13): their poorest performance was observed in the BST alone session. Moreover, when BST was added to PEMI, individuals of the CTL group significantly increased their COX compared to baseline (103.46 ± 3.14%), whereas this capacity was impaired in MS people (102.37 ± 2.46%). It was concluded that: (1) MS affects cognitive performance; (2) people with MS were able to enhance COX during exercise, but they impair their COX when an attentional interference task was added.

Keywords: metabolic syndrome, exercise, cognitive processes, NIRS, attentional task

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INTRODUCTION

The metabolic syndrome (MS) is a cluster of interrelated conditions, increasing the risk of heart disease, heart disease, Type 2 diabetes mellitus, and stroke, among other health problems. The International Diabetes Federation estimated that 20–25% of the global adult population suffers from MS (International Diabetes Federation, 2015), which increases in older adults, but rates of MS ranging between 0 and 19.2% were also reported among children and adolescents (Friend et al., 2013). According to clinical guidelines, an individual suffers from MS if three or more risk factors

as high blood glucose, high blood pressure, high plasma triglycerides, high waist circumference, and low HDL cholesterol are present (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001; Alberti et al., 2009).

The MS has been correlated to cognitive dysfunction and poor performances in multiple domains as processing speed, memory, semantic fluency, visuo-spatial abilities, sustained attention, and executive function (Yaffe et al., 2004; Segura et al., 2009; van den Berg et al., 2009; Solfrizzi et al., 2011; Yates et al., 2012; Wooten et al., 2019). In order to explain the effects of MS on cognitive impairments different risk factors such as neuroinflammation, oxidative stress, impaired vascular reactivity, and abnormal brain lipid metabolism have been taken into account (Yates et al., 2012).

Although every single risk factor plays some role in the decline of cognitive function, the question was raised as to whether these risk factors taken together have a higher predictive value for cognitive deterioration. Cohort studies with cross-sectional research designs (Yaffe et al., 2004; Segura et al., 2009; Vieira et al., 2011) or longitudinal (Yaffe et al., 2009; Akbaraly et al., 2010) build a strong case for MS being associated with poor cognitive performance than its individual components. MS is mostly associated with impaired executive functioning, among all reported deficits (Wooten et al., 2019), although findings are mixed, with some cross-sectional studies reporting no effects (Tournoy et al., 2010; Kim et al., 2011) or even better cognitive performance among older women suffering from MS (Laudisio et al., 2008). Clearly, some of the ambiguity in the results obtained could be the effect of methodological issues as cognitive domains selected, demographic characteristics (i.e., differences in age, race, gender, educational level, and socioeconomic position), MS status vs. persistent MS, health status of experimental and control group, and complexity in splitting the impact of individual factors from that of the MS itself (Akbaraly et al., 2010); further studies incorporating some protective factors have been also claimed (Yates et al., 2012).

The vascular risk factors as, for example, high blood sugar and low level of HDL cholesterol, are all potentially reversible and current recommendations for the treatment of MS encourage intensive therapeutic lifestyle changes such as increasing regular physical activity and reducing the dietary intake of saturated fat and cholesterol. Regular physical activity of moderate intensity can reduce singular metabolic risk factors while benefits of exercise on multiple risk factors were also reported (Laaksonen et al., 2002; Katzmarzyk et al., 2003; Holme et al., 2007). Previous researches show evidence that a lower prevalence of MS is associated with at least 150 min weekly of moderate-intensity PA (Strasser, 2013). However, to appreciate the benefits of movement it is relevant to distinguish among physical activity and exercise: while physical activity refers to any movement produced by skeletal muscles that require energy, exercise enhances the capacity and efficiency of the cardiorespiratory system and muscular strength associated with health and functional capacity (Caspersen et al., 1985). Improvements in fitness are noticeable in enhancement in executive-control processes such as, inhibition, planning, scheduling, coordination, and working memory. Due to brain activation and to the increase of cerebral blood flow (CBF) exercise may be therefore beneficial to reduce cognitive impairment (Secher et al., 2008; Kim et al., 2011). Interventions, such as exercise training programs, increase the cognitive performance of one-half standard deviation on average, regardless of the type of training method, cognitive task, or participants' characteristics (Colcombe and Kramer, 2003). Other potential mechanisms that account for the cognition-enhancing effects of exercise encompassed vascularization, neuroendocrine response to stress, neuroinflammation, brain amyloid burden, or other favorable effects on neuronal survivability and function (Baker et al., 2010).

Moreover, muscle metaboreflex activated by metabolites accumulating in the muscle during contraction can enhance the sympathetic tone and consequently the sympathetic nervous system (SNS) activity (Boushel, 2010). However, in people with metabolic disorders impaired CBF was reported whether caused by exercise (Kim et al., 2015; Vianna et al., 2015) or by stimulation of metaboreflex (Delaney et al., 2010; Milia et al., 2015; Crisafulli, 2017). Consequently, we have assumed that exercise is a critical factor for MS people's vulnerability to cognitive dysfunction, because may support cognitive functions, but limited physical activity and impaired CBF after exercise has been reported by individuals suffering from MS. When cerebral oxygenation (COX) is reduced after exercise (or stimulation of metaboreflex) cognitive functions can deteriorate and people experience early fatigue (González-Alonso et al., 2004; Rasmussen et al., 2010). Subclinical alterations in cerebrovascular reactivity and cerebral metabolism may denote early brain compromise associated with peripheral metabolic disturbances (Yates et al., 2012). Individuals with MS may not be able to retain an optimal neuronal environment, mostly when a high demanding cognitive task is superimposed to exercise. We hypothesized therefore that the association between metaboreflex and a contemporary mental task could result in an impairment of cognitive performance and in a reduced COX, in people suffering from MS.

MATERIALS AND METHODS

Participants

Two groups of participants were enrolled:

- MS group: 13 patients [five women, mean ± standard deviation (SD) of the mean of age 52.9 ± 11.2 years], who received a diagnosis of MS from at least a year (range 1–6 years). To be included in the study individual have to present three or more of the following five metabolic factors: (1) waist circumference >102 and >88 cm for men and women, respectively; (2) high blood pressure (≥130/85 mmHg); (3) low HDL cholesterol (≤40 and ≤50 mg/dL in men and women, respectively); (4) high triglycerides (≥150 mg/dL); and (5) high fasting glucose level (≥100 mg/dL).
- Control (CTL) group: 14 age-matched healthy participants (six women, mean ± SD of age 50.8 ± 8.1 years), unaffected

by any metabolic disease as resulted from anamnesis and physical examination.

In addition to age ≤18 and ≥65 years, exclusion criteria encompassed significant medical disease that could interfere with the autonomic function. Smokers and individuals taking sympatho-mimetics, β-blockers, and/or tricyclic antidepressants were also excluded.

Procedure

After enrolment, participants attended the laboratory on two occasions: one preliminary baseline visit and one experimental phase.

Baseline visit: All participants received a medical examination with anamnesis, anthropometric measures (weight, height, body mass index, waist circumference, and body composition), ECG, and blood pressure. To assess physical capacity all participants performed a cardiopulmonary exercise test (CPT) on a cycle ergometer (CUSTO Med, Ottobrunn, Germany): maximum heart rate (HRmax), maximal oxygen uptake (VO2max), and maximum workload (Wmax) were recorded. During the baseline visit, the participants familiarized with the laboratory equipment and staff.

Experimental phase: this phase started after at least 3 days (range 3–7 days) from baseline visit and included in random order five sessions (**Figure 1**). All participants were randomly assigned to the following five sessions. All sessions were composed of four blocks each lasting 3 min, for a total of 12 min. Sessions were spaced by at least 15 min of recovery. Recovery was considered complete when the heart rate was not higher than 5 bpm compared with the pre-exercise level. Participants were requested to abstain from alcohol, caffeinated beverages, and heavy exercise for 12 h prior to coming to the laboratory.

This study was carried out in accordance with the recommendations of the Code of Ethics for Research in Psychology, Italian Association of Psychology. The protocol was approved by the ethics committee of the University of Cagliari. All participants gave written informed consent in accordance with the Declaration of Helsinki.

The experimental phase started after at least 3 days (range 3–7 days) from baseline visit and included in random order the following five sessions (**Figure 1**):

Specifically, sessions were as follows:

- Post-exercise muscle ischemia (PEMI): 3 min of resting, followed by 3 min of exercise, consisting of rhythmic (30 compressions/min). The handgrip was settled at 30% of the maximum previously assessed as the peak reached during five maximal compressions executed on a hydraulic dynamometer (MAP 1.1, Kern, Balingen, Germany). The exercise was followed by 3 min of PEMI on the exercised arm induced by rapidly inflating an upper arm biceps tourniquet to 50 mmHg above peak exercise systolic pressure. The cuff was kept inflated for 3 min. Three minutes of recovery was further allowed after the cuff was deflated, for a total of 6 min of recovery.
- Control exercise recovery (CER): the same rest-exercise protocol used for PEMI was performed followed by a CER of 6 min without tourniquet inflation. The CER session was employed to have a control recovery situation without metaboreflex activation.
- Mental task (MT): A computerized attentional interference test, the Bivalent Shape Task (BST) (Esposito et al., 2013), was used to test the ability to suppress interference. The BST asks the participant to decide whether a shape at the center of the screen is a square or a circle. The stimulus

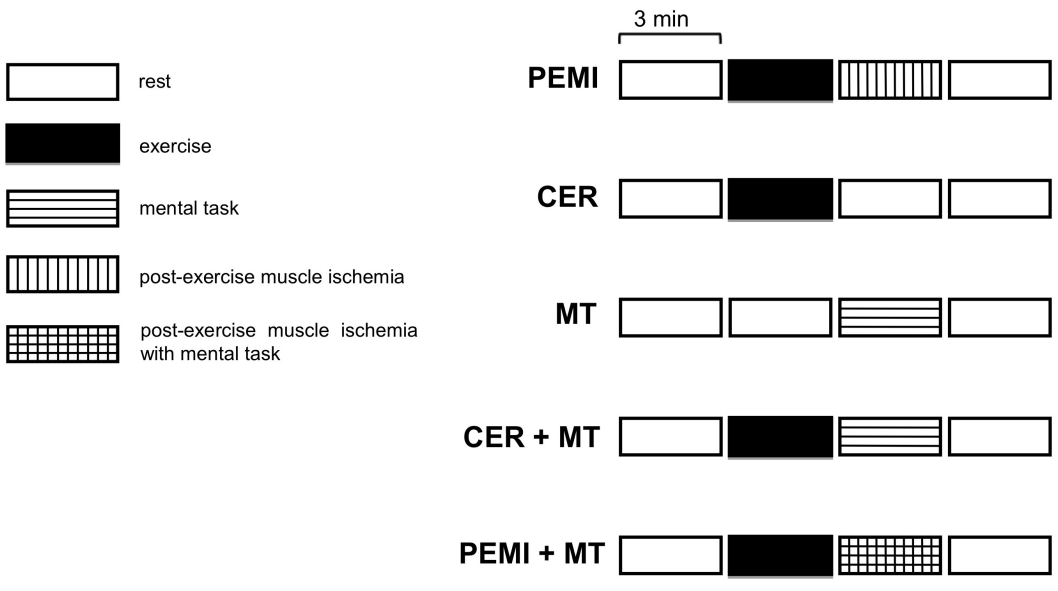

FIGURE 1 | Schematic representation of the various sessions of the study protocol. PEMI, post-exercise muscle ischemia; CER, control exercise recovery; MT, mental task; CER + MT, control exercise recovery + mental task; PEMI + MT, post-exercise muscle ischemia + mental task.

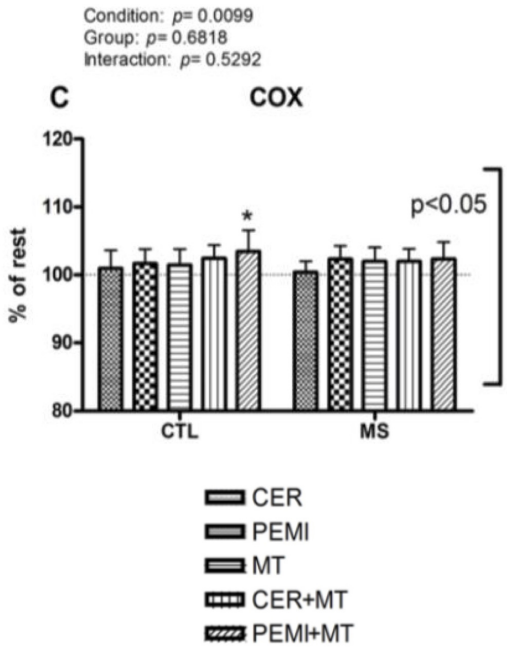

FIGURE 2 | Cerebral oxygenation data during control exercise recovery (CER), post-exercise muscle ischemia (PEMI), mental task (MT), control exercise recovery + mental task (CER + MT), and post-exercise muscle ischemia + mental task (PEMI + MT) tests in the metabolic syndrome (MS, $n = 13$) and the control (CTL, $n = 14$) groups. The dotted line indicates rest level. Values are mean ± SD. A horizontal bracket indicates the overall main effect of groups; a vertical bracket indicates the overall main effect of condition. $^*p < 0.05$ vs. CER test of the same group.

shape is presented either in blue, red, or an unfilled black outline. Visual response cues are provided below the stimulus, indicating the side of the response and are shaded in either red or blue. Three trial types were presented: neutral trials in which the stimulus is black and white; congruent trials, in which the (irrelevant) color of the stimulus matches the response cue; and incongruent, in which the (irrelevant) color mismatches the response cue. Compared to the condition in which the dominant response and the activated response are the same (e.g., congruent trials), a response interference is stimulated whenever the dominant response has to be suppressed in order to give the instructed response, as in the incongruent trials: this results in a deterioration of the performances. Dependent measures are the speed and accuracy with which participants take the decision: the speed was assessed in ms, the accuracy as percent of correct responses. The MT started after 6 min of rest and lasted for 3 min. Three further minutes of recovery was allowed after the termination of MT.

- CER + MT: the same rest-exercise protocol used for CER was performed. The exercise phase was followed by a MT session of 3 min, i.e., the same duration of the MT session described previously. Three further minutes of recovery was allowed after the termination of MT.
- PEMI + MT: the same rest-exercise protocol used for PEMI was performed. The exercise phase was followed by 3 min of contemporary PEMI and MT. Three further minutes of recovery was allowed after the termination of the PEMI + MT period.

Throughout sessions, COX was assessed by means of near infrared spectroscopy (NIRS; Nonin, SenSmart X-100, Plymouth, MN, United States), which provided a measure of oxygenated Hb in the brain tissue. It is recognized that changes in COX are representative of cortical activation (Strangman et al., 2002) and COX assessments by means of NIRS during mental tasks such as calculation, interference, or Stroop tasks were already reported (Plichta et al., 2006; Verner et al., 2013; Ferreri et al., 2014). Two NIRS sensors were placed on the right and left subject's forehead above the eyebrow, in the regions between Fp1 and F3 (international EEG 10–20 system) and adjusted according to the strong signal. Oxygenated Hb measured by NIRS can be considered an index of regional tissue blood flow as previously reported (Suzuki et al., 2004). Since the absolute concentration of oxygenated Hb could not be acquired, because the path length of NIRS light within the brain tissue was unknown, relative changes of NIRS signals against the baseline values were taken into account.

This study was carried out in accordance with the recommendations of the Code of Ethics for Research in Psychology, Italian Association of Psychology. The protocol was approved by the ethics committee of the University of Cagliari. All participants gave written informed consent in accordance with the Declaration of Helsinki.

Data Analysis

Preliminary analysis showed that all the BST protocols were valid with an accuracy of responses equal or above the predetermined threshold. A preliminary check of data, executed by means of the Kolmogorov–Smirnov test with Lilliefors correction that renders this test less conservative, has confirmed a normal distribution for all parameters examined. The *t*-test for independent groups was used to assess differences in anthropometric characteristics, levels of triglycerides, HDL cholesterol, fasting glucose, and results of the CPT. Two-way ANOVA (factors: group and condition) was executed to assess (a) response times (ms) on BST; (b) change in COX reported as % changes from rest. Statistics were carried out utilizing commercially available software (GraphPad Prism and SPSS ver. 17.0). Statistical significance was established as a *p*-value of <0.05 in all cases.

RESULTS

The protocol was completed by all participants none reported discomfort or unbearable pain during PEMI. Anthropometric characteristics of both groups together with results of the baseline visit are shown in **Table 1**.

Participants of the MS group had a higher weight, BMI, waist circumference, FM, SBP, DBP, and fasting glucose with respect to the CTL group. **Table 1** also shows that FFM, TBW, VO2max, Wmax, and HRmax were lower in the MS than in the CTL group.

TABLE 1 | Anthropometric characteristics of both groups together with results of the screening medical examination and of cardiopulmonary test.

Anthropometric characteristics	CTL	MS	*P*-value
Height (cm)	169.5 ± 10.29	165.92 ± 8.08	0.326
Body mass (kg)	69.45 ± 12.23	96.73 ± 14.13	< 0.001
Body mass index (kg/m^2)	24.03 ± 2.74	35.26 ± 5.65	< 0.001
Waist circumference (cm)	80.75 ± 9.85	113.58 ± 7.24	< 0.001
Fat mass (%)	21.8 ± 5.5	35.9 ± 7.3	< 0.001
Fat-free mass (%)	78.2 ± 5.5	64.1 ± 7.3	< 0.001
Total body water (%)	57.1 ± 4.5	47.3 ± 5.5	< 0.001
Systolic blood pressure (mmHg)	111.07 ± 9.84	123.85 ± 8.69	0.001
Diastolic blood pressure (mmHg)	73.57 ± 6.91	81.15 ± 6.50	0.007
Maximal O_2 uptake (mL/kg/min)	31.70 ± 9.36	19.99 ± 3.46	< 0.001
Maximum workload (W)	199.30 ± 84.39	140.76 ± 29.56	0.026
Maximum heart rate (bpm)	158.80 ± 12.45	147.84 ± 13.15	0.035

Values are mean ± SD. CTL = controls (n = 14), MS = Metabolic Syndrome patients (n = 13).

Table 2 shows that the significant differences between groups were found only in BST scores, while COX was significantly affected by the condition. In particular, MS group, compared to CTL group, performed significantly worse in all sessions were MT was included ($F = 4.18$; $p = 0.05$; ES = 0.13). In both groups, COX increased during the CER, the PEMI, the CER + MT, and the PEMI + MT tests compared to the MT test.

Moreover, when MT was added to PEMI, individuals of the CTL group significantly increased their COX compared to baseline (103.46 ± 3.14%), whereas this capacity was impaired in MS people (102.37 ± 2.46%, see **Figure 2**).

DISCUSSION

The management of chronic diseases requires to assume and maintain an active role centered on: (a) acquisition of self-regulated behavior; (b) suppression of interferent habitual response (such as sitting after meals); and (c) replacement of habit with other healthier behavior (such as going for a walk) (Settineri et al., 2019). Exercise appears to be a useful strategy to treat MS, because it could reduce cognitive impairment and risk to develop Type 2 diabetes mellitus, stroke, and heart diseases. However, adults with MS may be at increased risk of non-adherence exercise due to a concurring rise in behavioral requests (e.g., nutrition planning, glucose tracking, medication timing) and decrease in cognitive function (Olson et al., 2017). Compared to modifications of nutrition or taking medications, exercise requires more time to be practice and deliberate continuous effort of planning and monitoring: people suffering from chronic diseases often perceive its adoption as a significant and difficult change in their lifestyle (Guicciardi et al., 2014).

The principal aim of the present investigation was to characterize the mental performance and the COX in people suffering from MS during exercise, associating a mental task (BST) to metaboreflex activated by means of the PEMI method.

About the mental performance, significant differences in response times were found between groups: the participants suffering from the MS took longer to discriminate the shapes of BST. Compared to CTL group, their performances were always worse, supporting the hypothesis that MS can impair executive functions, such as interference suppression. The difference in cognitive performance due to MS was small (ES = 0.13); however, considering the high prevalence of MS, the burden of impaired cognition due to the MS may be substantial in the overall population (Vieira et al., 2011). The individuals suffering from MS may not be able to maintain an optimal performance during high demanding tasks as BST, which requires participants to control the interference due to the stimulus characteristic (e.g., color) and focus on the relevant information (e.g., shape) to give the correct response. Both groups have reported their poorest cognitive performance in the MT alone trial, but when PEMI or CER was superimposed their response times improved even if not significantly. As know, exercise has more effect on executive functions, than on any other type of cognitive process (Colcombe and Kramer, 2003); however, to evaluate concurrent improvements in other cognitive processes, such as working memory, sustained attention, or visuo-spatial abilities further researches should be conducted using more suitable tasks.

About the COX, participants suffering from MS, compared with healthy controls, were unable to increase COX when BST was superimposed to the PEMI-induced metaboreflex activation. This occurrence suggests that people suffering from MS were not able to increase COX to the same extent of CTL groups when a mental task was superimposed to the PEMI-induced metaboreflex activation. In both groups during the mental task, COX tended to slightly increase with respect

TABLE 2 | Bivalent shape test (BST) scores and cerebral oxygenation (COX) during the mental task (MT), control exercise recovery + mental task (CER + MT), and post-exercise muscle ischemia + mental task (PEMI + MT) tests for control (CTL, *n* = 14) and metabolic syndrome (MS, *n* = 13) groups.

Anthropometric characteristics	MT	CER + MT	PEMI + MT	*P*-value condition effect	*P*-value group effect	*P*-value interaction
BST (ms)	CTL 1020.05 ± 271.74	CTL 970.99 ± 271.74	CTL 987.15 ± 224.54	0.311	0.050	0.857
	MS 1249.00 ± 444.35	MS 1235.45 ± 380.69	MS 1201.96 ± 406.34			
COX (%)	CTL 100.79 ± 1.41	CTL 102.61 ± 1.56*	CTL 103.3 ± 2.09*	< 0.001	0.969	0.524
	MS 100.36 ± 1.10	MS 103.10 ± 2.89*	MS 102.54 ± 1.27*			

*Values are mean ± SD. *p < 0.05 vs. MT test of the same group.*

to the baseline. This MT-induced raise in COX was probably the consequence of the increased brain activity due to the mental task, which enhanced brain metabolism and led to COX elevation (Willie et al., 2014). All COX levels were similar among conditions with an exception: during the PEMI + MT test of the CTL group, COX was significantly more elevated than the baseline. This could demonstrate that adding a mental task to the PEMI-induced metaboreflex activation increased COX in normal individuals, but not in individuals suffering from MS, who were not able to increase COX to the same extent of CTL participants.

We examined the effects of experimental sessions on response times and we used these data to infer information about the brain mechanisms involved while performing a mental task during an exercise. We cannot provide any ultimate explanation for the lacking increase of COX in MS group when a mental task was superimposed to PEMI: individuals could have an elevated SNS drive which impaired the capacity to enhance COX or an impaired cerebral vascular reactivity or a reduced capacity to maintain COX at a proper level. Whatever the cause results suggest that individuals suffering from MS have impaired executive control and are unable to properly increase COX when a mental task activity was superimposed the metaboreflex obtained by means of PEMI maneuver. This phenomenon could explain why individuals suffering from MS do not meet physical activity recommendation, since executive functions are necessary for behavior change and can affect an individual's capability to successfully adopt and maintain physical activity behavior change (Olson et al., 2017).

Limitations of the Study

One possible limitation of this study is the response times of BST assumed as proxies to assess executive functions. Attention and processing speed are typically categorized as a general cognitive function; however, they are more related to executive function domain and to a successful behavioral change (Olson et al., 2017). The BST is an attentional test, where color and shape are varied within trials. The task is similar to other traditional interference tasks (e.g., the Simon interference task, the color-word Stroop test, and Eriksen's flanker task), but not prompts verbal reactions. The task was already used to assess the ability to suppress irrelevant information in non-linguistic settings, but more studies are required to validate this task with adults suffering from MS. Another possible limitation of the present investigation is that SNS activity was not directly assessed. This kind of measure are somewhat invasive and not applicable in experimental settings such as the present one, with ongoing psychological stress. A further potential limit of this study is related to the use of NIRS, compared to other brain imaging techniques, such as transcranial Doppler (TCD) or functional magnetic resonance imaging (FMRI). Several studies have confirmed the sensitivity of NIRS to measure subtle changes in COX during arithmetic or neuropsychological tasks involving the frontal lobe such as Stroop test (Ferreri et al., 2014). However, NIRS suffers of low spatial resolution which makes difficult to detect changes in areas located distant from the monitored site. On the other hand, NIRS offers some advantages as portability, good motion tolerance, non-invasiveness, and low maintenance costs. A further limitation of this study is the small size of the sample of individuals suffering from MS, that asks for studies replications. Finally, we cannot exclude that asking participants to refrain from caffeinated beverages, alcohol, and heavy exercise for 12 h before the experimental phase, may have affected their routine, and therefore every participant's average performance.

CONCLUSION

In conclusion, the results of the present investigation provide evidence that individuals suffering from MS had worse cognitive performance, compared to control group, in an attentional interference task, which involves executive functions. Individuals with MS were able to enhance COX during handgrip and during the metaboreflex activation; however, they could not further enhance COX when a mental task was superimposed to the metaboreflex. This conclusion could be intriguing as it may provide a potential psycho–physio–pathological basis of the scarce predisposition to exercise often reported in people with MS, since metaboreflex and cognitive performance are both operating during exercise (Wasmund et al., 2002) and executive functions are necessary to initiate and maintain physical activity behavior change (Olson et al., 2017).

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

The final version of this manuscript was written by MG and AC who contributed equally to the theoretical and empirical aspects of the study. AD collected and analyzed the medical data and wrote a preliminary version of this manuscript. RL and DF, respectively, collected and analyzed the psychological data.

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frontiers in Psychology

ORIGINAL RESEARCH
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Emotional Suppression and Oneiric Expression in Psychosomatic Disorders: Early Manifestations in Emerging Adulthood and Young Patients

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Background: The function of emotions, beginning from the proto-emotions, is the adaptation to the environment. This is based on the *Homeorhesis*, the equilibrium due to the adaptive operation of excitement and the dissipation of emotions. The object relations of the participants foresee the practice of defense mechanisms in a continuum that goes from the consciousness to the oneiric activities. The predominant and maladaptive use of defense mechanisms in the psychosomatic phenomenology, can be identified with deficits in emotional awareness, with the impossibility to manage excitement and dissipation of emotions foreseen by the oneiric phenomena.

Methods: The observation group is composed by 140 participants, 56 males (43%) and 84 females (57%),with pathological-functional disorders of psychosomatic domain. The study had been conducted with the use of measures related to the conscious defense of suppression (Suppression Mental Questionnaire), to the emotional awareness linked to the psychosomatic phenomena (Diagnostic Criteria for Psychosomatic Research Structured Interview-DCPR-SI) and to the states of perturbation and conservation of oneiric activities (The Manheim Dream Questionnaire-MADRE).

Results: Significant inverse correlations emerged among rationalization, repressive function and illness Denial, as for the suppression mental questionnaire factors and irritable mood, but for Regression in the service of the Ego; inverse and significant correlations emerged among suppression, repressive function, rationalization and gastrointestinal psychosomatic outcomes and among suppression, repression and cardiological psychosomatic outcomes. Regarding alexithymia, a positive correlation emerged with rationalization and inverse with Regression in the service of the Ego. Positive correlations emerged between illness denial and overall emotional tone, for disease phobia and meaningfulness and for cardiological psychosomatic outcomes and nightmare distress and recurring nightmares.

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Conclusion: The study of such outcomes due to a prevalent defensive style based on suppression, suggest the identification of a key phenomenon, which translates into maladjustment that goes from functional disorders to parasomnia. The bridge established by the obfuscation of conscious contents until the manifestations of disturbance of ancient activities such as oneiric ones, expresses the need to transform an emotional maladaptive style, in line with classic literature and the current state of art.

Keywords: psychosomatics, suppression, dreams, psychological factors, emotional

INTRODUCTION

As suggested by Berney et al. (2014), the clinical study of defense mechanisms allows us to comprehend and to explain affective dynamics, particularly relevant in clinical and therapeutic fields. In line with other defense mechanisms, the suppression has an adaptive meaning when its use is well integrated and directed to the managing of environmental and inner necessities (Metzger, 2014) and it is considered as a mature defense (Perry, 1990; Vaillant, 2000; Perry and Henry, 2004). The use and the polarization on suppression is considered by classical psychosomatic research as the main psychological figure for the occurrence of relevant organic outcomes (Marty and Fain, 1952).

We assist to affective dynamics whose un-expression and difficulties in the mentalization processes, are then translated in body manifestations on target organs and tissues. Differently from other defense mechanisms, the particular constitution of suppressive functioning is based on the need to face conflicts consciously recognized, so that its use is common, conscious and familiar to everyone's daily life (De Burge, 2001; Settineri et al., 2016).

In this sense, the outcome of the dysfunctional defense use, finding an indirect expression for us known in the products as symbolization, functional disturbance and organic lesions. This particular body-mind dynamic, is close to the current topics of the body-mind problem (Motofei and Rowland, 2018) and the necessity to confront classical approaches to current research practices.

In this sense, some of the classical considerations treated relevant dynamics such as dream contents (Kupper, 1947; French and Shapiro, 1949; Levitan, 1978; Warnes, 1982), dreams preceding psychosomatic illness (Warnes and Finkelstein, 1971) and the failure of defense dynamics in dreams of psychosomatic patients (Levitan, 1981). Recent approaches allow us to maintain the strong basis of previous research (Settineri et al., 2018) with the help of technology and modern practices (Schredl et al., 2014; Settineri et al., 2016, 2019c).

With particular attention to early psychosomatic manifestations and periods preceding somatic crisis, it is known in past literature, how psychosomatic illness is a substitute and following concomitant during emotional states of anxiety, depression, anger, guilt, and fear (Warnes and Finkelstein, 1971; Merlo et al., 2018; Vicario et al., 2019). Dreams are triggered by this emotional state, which in turn facilitates somatic reactivity in predisposed individuals. As for the conscious nature of suppression, the study of dream through consciousness is possible with the empirical research on recall phenomena (Cory et al., 1975; Cernovsky, 1984; Schredl and Engelhardt, 2001; Beaulieu-Prévost and Zadra, 2005; Schredl, 2007; Schredl and Göritz, 2015; Mangiaruga et al., 2018) and with reference to their characteristics and contents (Schredl, 2010). As for the relevance of dream recall, the presence of maladjustment in psychopathological conditions is also expressed through oneiric manifestations (Schredl and Engelhardt, 2001; Llewellyn and Desseilles, 2017; Aviram and Soffer-Dudek, 2018), such as nightmares (Schredl and Göritz, 2018) since childhood to adulthood (Kajeepeta et al., 2015) and above mentioned relevant characteristics of dreaming.

Currently, the need of providing new research instruments close to the purpose of clinical psychology in psychosomatics, was foreseen by the integration of those phenomena that go beyond the nosographic framework (Porcelli and Rafanelli, 2010; Fava et al., 2017). As suggested by Porcelli and Rafanelli (2010), the use of certain psychodiagnostic instruments allow us to diagnose from 2 to 3 syndromes that are not diagnosable with DSM. A particular interest is due to alexithymia, whose relevance has a long history in literature and strong evidence in clinical and neuroscientific contexts (Tesio et al., 2019). The same authors suggest a prevalence psychosomatic syndromes in different clinical settings, such as Dermatology (Picardi et al., 2006), Cardiovascular (Grandi et al., 2001; Rafanelli et al., 2003, 2006), Gastrointestinal (Porcelli et al., 2000; Carrozzino and Porcelli, 2018; Kano et al., 2018), and others.

The Current Study

The scope of this study was to highlight the characteristics related to the role of different factors of suppression and their outcomes through the revelation of oneiric perturbation and pathological psychosomatic phenomena.

Hypothesis:

HP-1 we hypothesize that different Suppression factors are significantly and inversely (−) associated with the Psychosomatic Syndromes and the pathological diagnosed groups;

HP-2 we hypothesize that the different Psychosomatic Syndromes are significantly and positively associated with Oneiric phenomena, plus the pathological diagnosed groups;

MATERIALS AND METHODS

Procedure and Participants

The observation group consists of 140 participants, 56 males (43%), and 84 females (57%). The age of the participants included in the study is between 19 and 30 years old, with an average of 23.58 years (SD = 2.06).

The research was carried out within the UOC of Psychiatry of the University Hospital G. Martino of Messina.

The participants of the research were considered on the basis of the diagnosed psychosomatic clinical reality, of the related evident psychological components and subsequently subjected to psychodiagnostic practice.

The participants were invited to continue the diagnostic process in order to produce clinical evidence, useful to highlight the psychological characteristics underlying the recognized medical condition and to use the data for research.

The study with the participants and the subsequent diagnostic phases lasted about 2 h for each patient. The compilation of the questionnaires was of a paper and pencil type and each participant before the signing of the informed consent was informed about the anonymous nature of the methods of data processing, as required by the procedures of the ethical committee evidenced by the approval.

Statistical Analysis

The numerical data were expressed as mean and standard deviation and the categorical variables as number and percentage.

The Spearman test was applied in order to evaluate the correlation among Suppression, Dream and Psychosomatic variables of the following instruments.

Statistical analyses were performed using SPSS 20.0 for Window package.

A *P*-value smaller than 0.050 was considered to be statistically significant.

Instruments

Suppression Mental Questionnaire

The suppression metal questionnaire was developer in 2016 by Settineri et al., it provide for a total score about Suppression and three factors, respectively, Repressive function, Regression in the Service of the Ego and Rationalization. An app version was also developed in 2019 (Settineri et al., 2019c).

The Mannheim Dream Questionnaire was developed by Schredl et al. (2014). An Italian adaptation of the questionnaire was provided by Settineri et al. (2019a). The instrument involves 20 factors about dreams and related phenomena. In this study the selected items were: Overall Emotional Tone, Nightmare Frequency, Nightmare Distress, Recurring Nightmares, Percentage of recurring Nightmares, Meaningfulness.

The reliability indexes of the considered Madre items (Dyck et al., 2017; Settineri et al., 2019a) are reported below.

Overall Emotional Tone:0.764 (0.708 to 0.797)
Nightmare Frequency:0.876 (0.843 to 0.918)
Nightmare Distress:0.823 (0.754 to 0.901)
Recurring Nightmares:0.899 (0.825 to 0.958)
Percentage of recurring Nightmares:0.971 (0.962 to 0.984)
Meaningfulness:0.775 (0.687 to 0.869)

Diagnostic Criteria for Psychosomatic Research (DCPR), is a clinical interview based on diagnostic criteria provided by Fava et al. (1995) whose structured interview is contained in the monograph by Porcelli and Sonino (2007); a set of 12 syndromes was provided: disease phobia, thanatophobia, health anxiety, illness denial, persistent somatization, functional somatic symptoms secondary to a psychiatric disorder, conversion symptoms, anniversary reaction, irritable mood, type A behavior, demoralization, and alexithymia. According to Galeazzi et al. (2004) the items of the DCPR showed a high showed interrater reliability with kappa values:

Disease phobia, kappa 0.97; Thanatophobia, kappa 0.92; Type A behavior, kappa 0.92, Illness denial, kappa 0.90; Demoralization, kappa 0.90; Anniversary reaction, kappa 0.90; Health anxiety, kappa 0.89; Alexithymia, kappa 0.89; Conversion symptoms, kappa 0.82, Persistent somatization, kappa 0.70; Irritable mood, kappa 0.69.

RESULTS

Descriptive Statistics

Descriptive statistics (mean and standard deviation) were reported in **Tables 1**–**3**, in order to highlight the presence of considered phenomena.

Hypothesis 1:

As regards the hypothesis 1 and as shown in **Table 4**, we found significant inverse correlations among Rationalization, Repressive function and Illness Denial, suggesting that decreasing level rationality and suppression corresponds to increasing denial level about diseases consideration and fear.

TABLE 1 | Suppression Mental Questionnaire factors and total score mean and standard deviation.

	Mean	Standard Deviation
SMQ Total Score	47.78	7.24
Repressive Function	21.20	4.69
Regression in the service of the Ego	16.60	4.16
Rationalization	13.95	2.69
Razionalization and Repressive Function	31.29	5.90

TABLE 2 | Mannheim Dream Questionnaire-Italian Adaptation considered variables mean and standard deviation.

	Mean	Standard Deviation
Overall Emotional Tone	1.93	0.86
Nightmare Frequency	3.22	2.24
Nightmare Distress	1.56	0.87
Recurring Nightmares	0.38	0.86
Percentage of recurring Nightmares	17.35	17.64
Meaningfulness	1.83	1.00

TABLE 3 | Diagnostic Criteria for Psychosomatic Research (DCPR) frequency and percentage (*N* = 140).

	Frequency	Percentage
Health anxiety	123	87.9%
Disease phobia	69	49.3%
Thanatofobia	65	46.4%
Illness denial	62	44.3%
Functional somatic symptoms secondary to a psychiatric disorder	97	69.3%
Persistent somatization	100	71.4%
Conversion symptoms	66	47.1%
Anniversary reaction	57	40.7%
Type A behavior	136	97.1%
Irritable mood	102	72.9%
Demoralization	99	70.7%
Alexithymia	81	57.9%
Dermatological outcomes	117	83.6%
Gastrointestinal outcomes	127	90.7%
Cardiological outcomes	112	80.0%

Higher scores on Suppression mental questionnaire were associated with lower scores on irritable mood, but for Regression in the service of the Ego. In particular, the increase of Suppression, Repressive function and Rationalization suggest that rational practices related to thought correspond to decreasing irritable mood, anger, and other related phenomena.

Contrary to what emerged about conscious attempts to reduce irritability, the practice of fantasy and inner images as a way to have a deeper understanding of unconscious figures, has an increasing direction as for irritable mood. In this sense, the knowledge about the role of conscious defense such as suppression, confirm the phenomenology of decreasing affective dynamics and mood regulation.

In line with what emerged, Rationalization and Regression in the service of the Ego represent two opposite dynamics. Referring to their relation with Alexithymia, a positive correlation with Rationalization and an inverse relation with Regression in the service of the Ego has emerged. In particular these relations suggest that the non-rationality of the unconscious contents related to emotions are associated with the decreasing of Alexithymia and that a more rational approach to emotions and affectivity is closer to emotive crystallization.

In reference to the use of rationality treating emotions, negative significant correlations emerged among Suppression, Repressive function, Rationalization and Gastrointestinal psychosomatic outcomes. In the same way, negative significant correlations emerged among Suppression, Repression and Cardiological psychosomatic outcomes. In this sense, the directions assumed by the phenomena would inform us about the defensive value of the suppression and the associated phenomena. Specifically, the conscious dynamics linked to pathological outcomes, images and emotions were associated with attempts at adaptation that were still functional for the participants. This is to be considered with respect to the peculiarities of the participants, in their early psychosomatic manifestation. This would represent a good psychotherapic index, designed to avoid a crystallization on certain defense mechanisms (which then turns out to be dysfunctional) and the enrichment of adaptive modalities and management of disease representations.

Hypothesis 2:

As regards the hypothesis 2 and as shown in **Table 5**, we found that the results involving psychosomatic syndromes and dream outcomes demonstrate positive and significant correlations among Health anxiety with Recurring nightmares, the Percentage of Recurring Nigtmares and Disease Phobia with Meaningfulness.

TABLE 4 | Correlation coefficients among SMQ and DCPR variables.

	SMQ Total Score	Repressive Function	Regression in the service of the Ego	Rationalization	Rationalization and Repressive Function
Health anxiety	0.054	−0.028	0.106	0.019	−0.012
Disease phobia	−0.060	−0.110	0.127	−0.087	−0.107
Thanatofobia	−0.021	−0.010	−0.005	−0.049	−0.013
Illness denial	−0.132	−0.136	0.020	−0.162	−0.181*
Functional somatic symptoms secondary to a psychiatric disorder	0.022	−0.012	0.091	−0.062	−0.018
Persistent somatization	−0.085	−0.010	−0.128	−0.056	−0.023
Conversion symptoms	−0.017	−0.030	0.029	−0.035	−0.029
Anniversary reaction	−0.015	−0.030	0.099	−0.045	−0.056
Type A behavior	−0.055	−0.076	0.028	−0.108	−0.091
Irritable mood	−0.198*	−0.257**	0.203*	−0.301**	−0.302**
Demoralization	0.000	−0.091	0.152	0.051	−0.069
Alexithymia	0.014	0.091	−0.185*	0.176*	0.146
Dermatological outcomes	−0.018	−0.057	0.35	−0.067	−0.079
Gastrointestinal outcomes	−0.236**	−0.230*	−0.016	−0.123	−0.223**
Cardiological outcomes	−0.278**	−0.312**	0.035	−0.129	−0.284**

*$p < 0.05$ (two-tailed); **$p < 0.01$ (two-tailed).

TABLE 5 | Correlation coefficients among DCPR and Madre variables.

	Overall Emotional Tone	*Nightmare Frequency*	Nightmare Distress	Recurring Nightmares	Percentage of recurring Nightmares	Meaningfulness
Health anxiety	−0.120	−0.008	0.055	−0.017	0.177*	0.026
Disease phobia	−0.002	0.136	0.102	0.136	−0.023	0.216*
Thanatofobia	−0.207*	−0.060	−0.009	0.045	0.076	0.074
Illness denial	0.180*	0.107	0.122	−0.107	0.066	0.019
Functional somatic symptoms secondary to a psychiatric disorder	0.054	0.024	0.068	0.029	−0.017	0.052
Persistent somatization	0.139	−0.015	−0.086	0.008	0.001	0.036
Conversion symptoms	0.004	0.132	0.001	0.095	0.045	0.004
Anniversary reaction	0.092	−0.200*	0.028	0.035	−0.029	0.059
Type A behavior	0.023	0.078	0.069	−0.061	−0.001	0.095
Irritable mood	−0.071	−0.092	0.088	0.076	−0.003	0.122
Demoralization	−0.122	0.149	−0.026	−0.026	−0.014	−0.123
Alexithymia	−0.160	0.002	−0.057	−0.057	0.059	−0.088
Dermatological outcomes	−0.114	0.017	0.038	0.038	−0.059	−0.049
Gastrointestinal outcomes	−0.049	0.079	0.114	0.114	−0.006	0.013
Cardiological outcomes	0.061	0.166	0.177*	0.177*	−0.098	0.069

*$p < 0.05$ (two-tailed); **$p < 0.01$ (two-tailed).

In particular, considering the participants involved in this study with their early psychosomatic manifestations, these results show that at the beginning of the somatic manifestations we assist to an association linked to health and corporeal anxiety and the oneiric disturbance.

Beyond the highlighted associations, it is known as the managing of excitement and the dissipation of emotions ceases to be adaptive in pathological experience.

In the same direction, Illness Denial and Overall emotional tone were in a positive relation, suggesting the direction of emotions involved in this interruption of the adaptive managing of emotions. As for other relevant phenomena, the meaning related to dreams and to experience have a strong role in the adaptation processes. In particular, a positive correlation emerged between Disease Phobia and Meaningfulness, where the increase of phobias related to health and diseases corresponds to the increase of search for meaning.

In line with oneiric disturbance, Cardiological psychosomatic outcomes had positive associations with Nigtmare Distress and Recurring Nightmares, in order to confirm the relevance of dreaming related to the perception of somatic anguish and agitation.

DISCUSSION

The current study was aimed at highlighting the relationships between emotional suppression and typical oneiric expressions in psychosomatic individuals in their first pathological manifestations.

For this reason, the choice to use specific instruments for the phenomena expressed, was been extended to participants who experimented pathological experiences of dermatological, cardiological and gastroenterological domain. The results showed that it was possible to observe phenomena related to emotional suppression in association with psychosomatic dynamics and between dream expressions and disorders mentioned above. In support of the first hypothesis of this study, we found an inverse general trend was found regarding the practice of emotional suppression, in relation to specific psychosomatic realities and large diagnostic groups. Considering the different nature between the first two factors of repression and the regression in the service of the Ego (less conscious fantasies), an important datum emerged in relation to the continuous and positive trend of the aforementioned dynamic and psychosomatic factors. In our research experience and in line with what was expressed in the results, conscious attempts to stem the psychosomatic experience appear in a reverse and therefore functional direction. In support of the second hypothesis, regarding oneiric manifestations we found dysfunctional experiences emerged in positive association with psychosomatic pathological experiences. Nightmares and dysfunctional emotionality emerged positively associated with specific psychosomatic dynamics and in particular (recurrence of nightmares) with cardiac disorders.

It is known how hard the impossibility to distance ourselves from pathological phenomena can be, such as psychosomatic ones, since childhood (Szwec, 2018). Our experience was referred to participants in their early pathological manifestations and to the reasons for symptom formation, all conflicts, defenses and previous traumatic experiences (Wolf et al., 2018). The main scope of this research was to highlight directly and undirectly related phenomena, in order to prevent the typical loss of an adaptive Self (Marchini et al., 2018) and psychological manifestations whose mechanisms can predict the serious incoming pathological realities, their complex denial (Livneh, 2009) and subsequent decreasing quality of life and body satisfaction (Guicciardi et al., 2014; Catalano et al., 2018; Martino et al., 2018) for both patients and caregivers (Ferrario et al., 2017; Settineri et al., 2019b).

In our experience, rationality and conscious suppressive functions emerged as opposite to denial phenomena, so that the defense function appears as an adaptive way to manage emotions related to the pathological reality. This result was in line with recent perspectives about denial, where the managing of negative emotions due to the onset of pathological manifestations, together with resistance to change, represent a relevant step in the conscious elaboration of disease (Nowak et al., 2015; Ferrario et al., 2017).

As suggested by Ferrario et al. (2017) the unconscious nature of defense mechanisms, different to coping strategies, is unintentionally (Cramer, 2000). Our case involved a conscious phenomenon, so the inverse relation between suppression and denial confirm the distance and the effect that each factor had on the other.

As for the unconscious nature of denial, the reasons on the basis of mood misadjustment can be unknown. The role of suppression on negative emotions, such those related to irritability and anger, was found as relevant in our experience. As suggested by Wolf et al. (2018), the onset of somatic symptoms involves different defense mechanisms, useful to manage emotional distress.

In particular neurotic manifestations such as irritability, tension, anxiety, impulse have the role to avoid intolerable feelings. The role of the studied factors in our contributions, distinguishes between defenses closer to consciousness and others, related to unconscious necessities. In line with the emerged results in the case of denial, even for irritable mood, the role of rational functions has an effective decreasing role, contrary to regression dynamics. In our experience, the role of fantasy and rationality changes in front of alexithymia and his relation with physical illness (Porcelli and Taylor, 2018).

According to Porcelli and Taylor (2018), the role of alexithymia in the production of somatic symptoms is relevant. As for the inverse effect of suppression on alexithymia (and the positive effect of fantasy and regression in the service of the Ego), the results highlighted the same dynamic also extended to gastrointestinal and cardiovascular disorders, according to Porcelli and Taylor and the above-mentioned literature about somatic symptoms and research methodology.

With particular reference to those pathological psychosomatic outcomes, other relationships emerged in term of oneiric manifestations. Health anxiety and illness denial were directly related to nightmares, in terms of recurring phenomena and emotional tone. The link between nightmares distress and frequency with psychosomatic manifestations is known in literature (Nguyen et al., 2002; Fantoni et al., 2007; Molina et al., 2016).

In our experience the central emotive core of fear about diseases, involved the search of sense and meaning, as expressed by dreams (Levitan, 1976), as highlighted by the relation between the conscious consideration of anniversaries and the decreasing manifestation of nightmares. In line with the above-mentioned considerations about the innovative use of instruments related to psychosomatics, we suggest our research experience, as linked to the integration and promotion of psychodynamic phenomena, before less considered clinically and psychometrically. Our direct experience with the construction of a psychometric instrument linked to suppression is close to this purpose. The use of this instrument represented a clinical consideration specifically dedicated to the primary phenomena associated with suppression and consequently to psychosomatics.

Limitations and Conclusion

This study has a diversity of limitations that should be overcome in future studies. Besides the small sample size (140 participants), we assist just to the early psychosomatic manifestations in our young patients. This fact can be read through two opposing points of view. The first concerns this precise study, in which the first pathological manifestations are still not chronic and structured, although there are significant physical outcomes. This state is justified by the difficulty to express disturbing contents, which justifies the use of projective methods. Through the use of pareidolia and apperception (respectively, for Rorschach and Thematic Apperception Test) we reach equivalents whose revelation is due to the indirect request. The use of scales and psychometric measures is always useful, more with large samples and advanced pathological realities. The second point of view concerns the occasion given by this kind of studies, in terms of psychotherapy interventions. More advanced pathological states give light to a large number of relations among different variables, even if it could be harder to intervene on the phenomena in progress. Our purpose is referred to young patients, and in particular to the possibility to notice those phenomena on which it is possible to intervene instantly.

Further studies should focus in particular on investigating the relationships emerged, and should explore the causal links for which the outcomes we are witnessing are structured.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was approved by the local Institutional Ethical Committee. All the participants gave their consent to participate in this study and were evaluated by the clinical psychologists and physicians. This research was conducted with respect for the rights of the participants, according to the World Medical Association Declaration of Helsinki and its amendments. All administered instruments, including questionnaires, rating scales, and clinical structured interviews, were performed as a part of normal clinical practice assessment of patients. The data was analyzed anonymously. Each participant was properly informed about the research aim and study, and after comprehension signed the informed written consent.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. SS made significant contribution to design the research study, and draft the manuscript and revise it critically. FF provided substantial contribution in drafting the part of the manuscript. AA performed the statistical analysis and provided significant contribution to draft the part of the manuscript. EM made significant contribution to design the research study, provided the interpretation of data, a substantial contribution to draft the manuscript, and gave the final approval.

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Depression According to ICD-10 Clinical Interview vs. Depression According to the Epidemiologic Studies Depression Scale to Predict Pain Therapy Outcomes

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Purpose: Pain and depression have been shown to have a bidirectional interaction. Although several outcome studies have been conducted, it is still unclear if and how depression influences pain outcome. The current study aims to further clarify this relationship by comparing the predicting value of an interview- and a questionnaire-based assessment of depression.

Patients and Methods: This retrospective study analyzed data of $N = 496$ chronic pain patients who received a multimodal pain management program. Multilevel models were performed with depression as predictor, pain measures as dependent variables, and the respective pain score at baseline as covariate. Depression was measured at baseline with (1) a semi-structured psychiatric interview corresponding to the ICD-10 and (2) the Center for Epidemiologic Studies Depression Scale (CES-D). Pain outcomes were pain intensity assessed with the Numeric Rating Scale (NRS), pain disability measured with the pain disability index (PDI), and affective as well as sensory pain perception assessed with the Pain Perception Scale (PPS-A/PPS-S).

Results: At post-treatment, pain intensity (NRS) was higher in patients with depression. This result emerged for interview- (ICD-10) and questionnaire- (CES-D) based depression. These results were significant after correction for multiple testing as well. Moreover, affective pain perception (PSS-A) at post-treatment was higher in patients with depression. Again, this result emerged for interview- (ICD-10) and questionnaire-(CES-D) based depression but it was not significant anymore after correction for multiple testing. Furthermore, pain disability (PDI) was higher at post-treatment in patients with depression according to the CES-D than in those without CES-D depression and this difference in the PDI did not emerge for interview-based depression. Yet, this difference on the PDI between the CES-D depression group and the CES-D no depression group was not significant anymore after correction for multiple testing.

Conclusion: The hypothesis that how depression is assessed – interview-based corresponding to the ICD-10 or with the CES-D – contributes to the association between depression and pain treatment outcome could not be confirmed. Future research should use more than one interview and questionnaire to assess depression, since our results are limited to the clinical ICD-10 interview and the CES-D.

Keywords: mood disorder, self-assessment, evaluation, disability, interdisciplinary treatment

INTRODUCTION

A meta-analysis of epidemiological studies investigating chronic pain revealed prevalence estimates from 8.7 to 64.4 percent depending on how chronic pain was defined (Steingrímsdóttir et al., 2017). Lifetime prevalence of pain complaints ranges from 24 to 37% (Bair et al., 2003). Additionally, pain is the leading cause of years lived with disability (YLD), having low back pain causing 57.6 million and migraine causing 45.1 million of YLD in 2016 (Vos et al., 2017). Major depression, also one of the five leading factors causing YLD (34.1 million) (Vos et al., 2017), is common among patients with chronic pain (Bener et al., 2013; Stubbs et al., 2017). For instance, a large study evaluating the world mental health surveys of multiple western as well as developing countries showed a pooled odds ratio for depression among pain patients of 2.3 (CI: 2.1, 2.5) (Demyttenaere et al., 2007). Similarly, a recent study revealed significant associations between severe pain and depression in 44 of 47 investigated low- and middle-income countries (Stubbs et al., 2017).

Furthermore, chronic pain patients with comorbid depression cause higher health care costs than chronic pain patients without depression (Rayner et al., 2016). Additionally, depression frequency increases with higher age (Morete et al., 2018). Pain and depression also partly share the same neuronal processes, neurotransmitters, and brain structures (Sheng et al., 2017). For example, monoamine neurotransmitters as well as glutamate have been shown to be critically involved in the development of both pain and depression. Chronic pain also potentially reduces dopamine activity, which in turn is involved in the occurrence of depression (Sheng et al., 2017).

Moreover, medical treatment addressing depression has been shown to affect pain as well (Polatin et al., 2018). Medications reported to have both analgesic and psychotropic effects include SNRIs (serotonin norepinephrine reuptake inhibitors), TCAs (tricyclic antidepressants), and anticonvulsants (Hooten, 2016).

Due to the existing relationship between pain and depression, therapy programs are recommended to be multidisciplinary to address both disorders (Bair et al., 2003). Multidisciplinary pain treatment mostly consists of physiological, psychological, and social factors (bio-psycho-social model) (Gatchel et al., 2014). Physiological components address medication, exercise, surgery, sleep, psychological components address cognitions, emotions, behaviors, attention, social components address healthcare, family, and work. Typically, physicians, nurses, psychologists, physical therapists, and occupational therapists are involved in multidisciplinary pain management programs (Gatchel et al., 2014).

A review of McCracken and Turk (2002) revealed different predictors of the outcome of a behavioral and cognitive-behavioral pain treatment, including depression. However, the results on how depression affects the outcome of chronic pain treatments are ambivalent. While several studies found depression to be associated with a worse outcome (Betrus et al., 1995; Bair et al., 2003; Turner et al., 2007), others found that depression does not predict the outcome (Kerns and Haythornthwaite, 1988; Gureje et al., 2001; Glombiewski et al., 2010; Broderick et al., 2016). One study even reported that depression was associated with a better pain outcome (van der Hulst et al., 2008).

One reason for the diverging results may be the use of different methods to assess depression. Many studies used questionnaires to measure depression (Kerns and Haythornthwaite, 1988; Betrus et al., 1995; Turner et al., 2007; van der Hulst et al., 2008; Glombiewski et al., 2010; Broderick et al., 2016), which have economic advantages in being time-efficient and cost-effective (Stuart et al., 2014). Only a few used interview-based methods to assess depression (Gureje et al., 2001; Bair et al., 2003).

In general, structured interview-based methods reportedly best identify mood disorders (Stuart et al., 2014; Hooten, 2016). Questionnaires however, still show superiority in recognition of depression to physicians' depression diagnosis (Löwe et al., 2004) and have sensitivity rates between 25 and 100 and specificity rates between 22 and 99 (Löwe et al., 2004; Eaton et al., 2007).

In chronic pain patients, Poole et al. (2009) revealed comparable screening of interview-based depression and depression assessed with a questionnaire.

In summary, depression is a critical psychological aspect of chronic pain. Hence, depression, assessed either via questionnaire or interview, has been well-investigated as a predictor of pain treatment outcome. Although Poole et al. (2009) already compared both assessment methods, they did not include pain treatment outcome. To figure out whether the assessment method affects the connection between depression and pain treatment outcome, we investigated both questionnaire- and interview-based depression measurements in one sample.

The current study re-analyzed data of Pieh et al. (2012) who investigated gender differences in pain outcome after a multimodal pain management program. Pieh et al. (2012) found gender differences to have an influence on pain outcome after the therapy. In particular, pain-related differences in daily life were found to be better in women than in men after the therapy. The current study however, investigates differences between different depression measurements in pain outcome after the multimodal pain management program.

Our two research questions are: Is there a difference in the outcome of a multimodal pain management program (1) between patients with and patients without depression as assessed in interviews as well as (2) between patients with and patients without depression measured with a questionnaire?

The aim of this study is to investigate, if there is a difference between clinical interview-based ICD-10-corresponding depression and questionnaire-based depression according to the Center for Epidemiologic Studies Depression Scale (CES-D) in predicting pain outcomes. Furthermore, it aims at ascertaining whether one assessment method of depression is preferable for future research and clinical practice regarding the impact of depression on chronic pain.

As previous research showed ambivalent results with regard to the predicting value of depression on pain outcomes, we expected that interview- (ICD-10), and questionnaire- (CES-D) based depression differ in predicting pain outcomes.

MATERIALS AND METHODS

This is a retrospective study and a re-analysis of the data of Pieh et al. (2012). Data were collected from patients with chronic not malignant pain, treated in the pain clinic in Weiden, Germany, between 2006 and 2010. The study was conducted in accordance with the Declaration of Helsinki and ethical laws were applied. All participants signed a consensus declaration and agreed to the analysis of their anonymous data.

Depression Measurement

Semi-Structured Psychiatric Interview

Clinical diagnosis of depression was ascertained by specialists for psychiatry with a semi-structured psychiatric interview corresponding to the International Statistical Classification of Diseases and Related Health Problems (ICD-10) symptom checklist for mental disorders (Janca et al., 1994). The clinical diagnoses F32, F33, and F34.1 were categorized as existing depression diagnosis. Other clinical diagnoses were categorized as no depression diagnosis.

Center for Epidemiologic Studies Depression Scale (CES-D)

In the current study, we used the German version of the CES-D (Radloff, 1977) and accordingly the German cut-off of 22 recommended by Hautzinger (2016). The German CES-D matches the English Center for Epidemiologic Studies Depression Scale (Vilagut et al., 2016), which is often used for the operationalization of depression (Burke et al., 2015). For further analyses, we computed the sum value. The CES-D shows good reliability (Cronbach's Alpha > 0.90) and validity values (correlation with other self-rating instruments for depressive symptoms between $r = 0.64$ and $r = 0.88$) (Hautzinger, 2016).

According to the different depression measurements, four groups result (clinical interview-based depression: yes/no; CES-D cut-off exceeded; yes/no). However, considering our research questions, we compared participants with and without depression diagnosis for both measurements, respectively.

Pain Measurement

The following pain measures were administered at the beginning (t0) and end (t1) of the multimodal pain management program.

Numeric Rating Scale (NRS)

The Numeric Rating Scale is an often used self-rating instrument to measure pain intensity in chronic pain patients with a scale from 0 (no pain) to 10 (worst imaginable pain) (Joos et al., 1991; Jensen et al., 1999). It refers to the past 4 weeks and rates minimum, average, and maximum pain (Ferraz et al., 1990). In the current study, only the average pain rating was used. The NRS features good external validity in correlations with other pain intensity measurements (with e.g., VAS $r = 0.94$ to $r = 0.96$) (Williamson and Hoggart, 2005; Ferreira-Valente et al., 2011).

Pain Disability Index (PDI)

In the current study, the German version of the PDI (Dillmann et al., 1994) was used. This self-rating instrument assesses pain related disabilities on a rating scale from 0 (no disability) to 10 (full disability) in the following areas: recreation, social activity, responsibilities, occupation, self-care, sexual behavior, life support activity, and family/home (Tait et al., 1990). The German version of the PDI shows a good internal consistency (Cronbach's Alpha 0.88) (Dillmann et al., 1994), reveals a relatively low retest reliability ($r = 0.44$), and validation investigation showed relation to communicative behavior of pain patients (Tait et al., 1990).

Pain Perception Scale (PPS)

The Pain Perception Scale (Geissner, 1995) is a German instrument for measurement of both the affective (PPS-A) as well as the sensory (PPS-S) component of subjectively felt pain. Items are scored from 0 to 3 (from not to fully appropriate). The validated instrument shows internal consistency values between 0.72 and 0.92 (Cronbach's Alpha) (Geissner, 1996).

Mainz Pain Staging System (MPSS) (Gerbershagen, 1986)

At baseline, the Mainz Pain Staging System was used to assess the pain chronicity stage of the patients. The MPSS grades pain in terms of four pain-related axes: persistence, spreading, medication, and health care utilization. Stage 1 reflects mild chronicity, stage 2 moderate chronicity, and stage 3 severe chronicity. Construct validity of the MPSS has been shown, for example, by Frettlöh et al. (2003).

Treatment

Participants completed a multimodal pain management program, which was conducted by psychologists, physicians (a specialist for psychosomatic and psychotherapy, a neurologist and an anesthetist), physical therapists, relaxation therapists, a nutritionist, and a social worker. In accordance with the recommendation of Bair et al. (2003) the multimodal pain management program consisted of treatment of both pain and depression. Over 5 weeks groups of an average of 8 patients participated in an outpatient program (Monday to Friday) consisting of standardized group therapy and individual

treatment. The standardized group therapy comprised the CBT-oriented modules acceptance, stabilization, resolving conflicts and strengthening social competency, development of resources, as well as implementation in daily life (altogether 6 h per week). Additionally, the group treatment consisted of relaxation techniques (3.5 h per week autogenic training or progressive muscle relaxation), physical therapy (8 h per week), nutrition advice and social counseling (1 h per week), as well as pain education (2 h per week). The individual treatment contained physical therapy (0.5 h twice a week), doctor's appointment (0.5 h twice a week), and psychotherapy (1 h per week). In summary, every patient underwent 23.5 h therapy per week.

Statistics

Statistics were performed with SPSS25. The significance level was set at 0.05 and all statistical tests were performed two-tailed. For descriptive statistics we calculated mean (M), standard deviation (SD), and frequencies (*N*).

To evaluate differences in baseline variables between depressed and not depressed patients, *t*-tests for independent samples and chi-squared tests were calculated. To assess the pre-post effect of the multimodal pain therapy on pain outcomes (PDI, PPS-A, PPS-S, and NRS) in depressed vs. not depressed (CES-D or interview-based) participants, *t*-tests for paired samples were performed. Only patients with complete pre-post assessments were analyzed to examine the pre-post changes (missing data was not imputed for this analysis). Effect sizes (d) were calculated according to the following formula: (Mpre – Mpost)/SDpre. Effect sizes will be interpreted as small $d \geq 0.2$, medium $d \geq 0.5$, or high $d \geq 0.8$ effect.

To assess whether the effect of the multimodal pain therapy is associated with depression (research question 1, clinical interview-based depression; research question 2, depression according to CES-D cut-off), multilevel analyses were conducted with the post-values of PDI, PPS-A, PPS-S, and NRS as outcome variables. The full maximum likelihood method was used. Advantages of multilevel models over traditional methods like analysis of (co-)variance are less assumptions and more flexible handling of missing data. To address research question 1, clinical interview-based depression (yes = 1/no = 0) was entered as dichotomous factor and the pre-treatment scores of the respective pain rating were included as covariate. To address research question 2, the CES-D scores were dichotomized according to the cut-off [above/below cut-off 22 (Hautzinger, 2016)] and this CES-D-based depression variable (yes = 1/no = 0) was entered as dichotomous factor and pre-treatment scores of the respective pain rating as covariate.

Results are reported both without and with Bonferroni correction of the significance level.

RESULTS

Sample Description

Of the 496 included patients (254 women) 13 did not complete the treatment due to medical complications. Between 4 (ADS; 0.8% of the total sample) and 9 (PPS-S; 1.8% of the total sample) of the patients did not complete the measures at pre-treatment. Between 39 (NRS; 7.9% of the total sample) and 50 (PDI; 10.1% of the total sample) had missing values in the measures at post-treatment. **Table 1** shows the sample description and the comparisons in baseline variables for the sample divided by interview-based depression corresponding to the ICD-10. **Table 2** presents the sample description and the comparisons in pre-treatment variables for the sample divided by CES-D depression. Independent from the assessment method of depression (ICD-10 interview-based vs. CES-D questionnaire-based), depressed patients had higher pain chronicity (MPSS), higher pain disability (PDI), as well as higher affective (PPS-A), and sensory (PPS-S) pain at pre-treatment (all $p < 0.05$). Furthermore, the interview-based depression group had a longer pain duration than the no interview-depression group ($p < 0.05$) and this difference did not emerge between the CES-D groups. The CES-D depression group had a higher pain intensity and lower education than the CES-D no depression group (both $p < 0.05$) and these differences did not emerge between the interview-based groups.

Pre-Post Outcomes

Table 3 shows the results of the *t*-tests for paired samples evaluating the pre- and post-pain changes in patients with interview-based depression, in patients with no interview-based depression, in patients with CES-D depression, and in patients with no CES-D depression. All pain outcomes improved from pre- to post-treatment in each of these four groups ($p < 0.001$). Effect sizes were large for the NRS, medium for the PDI, and low for the PPS-S in each of the four groups. For the PSS-A, large effect sizes emerged in two groups (no interview-based depression; CES-D depression) and a medium effect size emerged in the other two groups (interview-based depression; no CES-D depression).

Research Question 1: Outcomes Subject to ICD-10 Interview-Based Depression

Results of the multilevel models controlling for the respective pain scale at pre-treatment are presented in **Table 4**. Before and after Bonferroni correction ($p < 0.05/4 = p < 0.0125$), the interview-based depression group scored higher on the NRS at post-treatment than the group with no interview-based depression ($p = 0.001$). The higher scores on the PPS-A at post-treatment for the interview-based depression group compared to the interview-based no depression group were significant before ($p = 0.028$) but not after Bonferroni correction.

Research Question 2: Outcomes Subject to Depression According to the CES-D

Results of the multilevel models controlling for the respective pain scale at pre-treatment are presented in **Table 5**. Before and after Bonferroni correction ($p < 0.05/4 = p < 0.0125$), the depressed group according to the CES-D scored higher on the NRS at post-treatment than the group with no depression according to the CES-D ($p = 0.005$). The higher scores on the PDI and the PPS-A at post-treatment for the CES-D depression group compared to the CES-D no depression group were significant before (PDI: $p = 0.018$; PPS-A: $p = 0.015$) but not after Bonferroni correction.

TABLE 1 | Comparisons in pre-treatment variables between depressed and not depressed patients according to clinical interview.

	Clinical interview		
	Depressed	**Not depressed**	**Statistics**
Gender n (%)			
Male	144 (47.8)	98 (50.3)	$\chi^2(2) = 0.28$; $p = 0.599$
Female	157 (52.2)	97 (49.7)	
Age (years)			
M (SD)	48.02 (±9.44)	49.17 (±10.92)	$t(493) = 1.24$; $p = 0.214$
Pain duration (months)			
M (SD)	92.67 (±84.14)	74.44 (±68.64)	$t(326.15) = -2.25$; $p = 0.025$
MPSS n (%)			
1 mild pain chronicity	1 (0.3)	11 (5.7)	$\chi^2(2) = 33.05$; $p < 0.001$
2 moderate pain chronicity	68 (22.7)	76 (39.2)	
3 severe pain chronicity	231 (77.0)	107 (55.2)	
Education n (%)			
<9 years	11 (4.7)	2 (1.5)	$\chi^2(3) = 3.78$; $p = 0.287$
9–10 years	207 (88.1)	124 (91.2)	
11–13 years	12 (5.1)	5 (3.7)	
>13 years	5 (2.1)	5 (3.7)	
NRS			
M (SD)	7.05 (±1.63)	7.01 (±1.78)	$t(489) = -0.23$; $p = 0.815$
PDI			
M (SD)	41.40 (±13.00)	36.87 (±13.63)	$t(488) = -3.70$; $p < 0.001$
PPS-A			
M (SD)	42.42 (±9.48)	38.95 (±8.87)	$t(489) = -4.06$; $p < 0.001$
PPS-S			
M (SD)	27.17 (±8.96)	24.41 (±9.06)	$t(485) = -3.31$; $p = 0.001$

MPSS, Mainz pain staging system; NRS, numeric rating scale of average pain intensity; PDI, pain disability index; PPS-A, pain perception scale affective; PPS-S, pain perception scale sensory; SD, standard deviation.

DISCUSSION

In the current study, we investigated the relationship between pre-treatment depression and pain outcomes after a pain treatment in chronic pain patients with regard to the way depression was operationalized (interview-based or questionnaire-based according to the CES-D). For pain outcomes, we investigated multiple pain dimensions (pain intensity, pain disability, affective pain, and sensory pain). The conducted pain treatment was a multimodal pain management program consisting of multiple treatment methods and was conducted by different physical and psychological specialists.

Although average pre-post effect sizes for changes in pain intensity were large, the results of the statistical models showed a difference in pain intensity (NRS) between pain patients with depression and those without depression. Pain intensity was higher at post-treatment in patients with depression. This result emerged for interview- (ICD-10) and questionnaire- (CES-D) based depression. These results were significant after correction for multiple testing as well. Additionally, affective pain perception was higher at post-treatment in patients with depression than in patients without depression. Again, this result emerged for interview- (ICD-10) and questionnaire- (CES-D) based depression but it was not significant anymore after correction for multiple testing. Moreover, pain disability (PDI) was higher at post-treatment in patients with depression according to the CES-D than in those without CES-D depression and this difference on the PDI did not emerge for interview-based depression. Yet, this difference on the PDI between the CES-D depression group and the CES-D no depression group was not significant anymore after correction for multiple testing. The findings for the PPS-A and the PDI are, therefore, not as robust as the results for the NRS. It should be kept in mind that the findings are correlational and should be interpreted with caution. Nevertheless, these results do not support our hypothesis that depression differentially predicts pain outcomes depending on the operationalization of depression. The NRS outcome was predicted by depression before and after correction for multiple testing regardless of how depression was assessed.

In the following paragraph, we embed our results in the literature. Previous studies using an interview-based depression assessment did not report worse pain outcome, but rather no association between baseline depression and pain outcome after pain treatment (Gureje et al., 2001). Studies using questionnaires to assess depressive symptoms on the other hand, found both negative, positive, and no correlation between depression and pain outcome (Kerns and Haythornthwaite, 1988; Betrus et al., 1995; Turner et al., 2007; van der Hulst et al., 2008; Glombiewski et al., 2010; Broderick et al., 2016). One reason for this incongruity may be the use of different

TABLE 2 | Comparisons in pre-treatment variables between depressed and not depressed patients according to self-assessment questionnaire (CES-D).

	CES-D		
	Depressed	**Not depressed**	**Statistics**
Gender n (%)			
Male	159 (48.3)	80 (49.1)	$\chi^2(1) = 0.03$; $p = 0.875$
Female	170 (51.7)	83 (50.9)	
Age (years)			
M (SD)	48.71 (±9.29)	48.00 (±11.44)	$t(271.02) = -0.69$; $p = 0.490$
Pain duration (months)			
M (SD)	90.75 (±83.16)	76.99 (±70.03)	$t(363) = -1.57$; $p = 0.118$
MPSS n (%)			
1 mild pain chronicity	4 (1.2)	8 (4.9)	$\chi^2(2) = 27.21$; $p < 0.001$
2 moderate pain chronicity	75 (22.9)	68 (41.7)	
3 severe pain chronicity	248 (75.8)	87 (53.4)	
Education n (%)			
<9 years	11 (4.5)	2 (1.6)	$\chi^2(3) = 8.23$; $p = 0.041$
9–10 years	220 (90.2)	110 (87.3)	
11–13 years	10 (4.1)	7 (5.6)	
>13 years	3 (1.2)	7 (5.6)	
NRS			
M (SD)	7.19 (±1.62)	6.72 (±1.80)	$t(486) = -2.91$; $p = 0.004$
PDI			
M (SD)	42.49 (±12.62)	33.71 (±13.12)	$t(485) = -7.15$; $p < 0.001$
PPS-A			
M (SD)	43.14 (±8.75)	36.93 (±9.37)	$t(486) = -7.22$; $p < 0.001$
PPS-S			
M (SD)	26.70 (±8.94)	24.98 (±9.28)	$t(482) = -1.97$; $p = 0.0498$

CES-D, center for epidemiologic studies depression scale; MPSS, Mainz pain staging system; NRS, numeric rating scale of average pain intensity; PDI, pain disability index; PPS-A, pain perception scale affective; PPS-S, pain perception scale sensory; SD, standard deviation.

TABLE 3 | Pre-post comparisons.

Group	**Outcome**	***N***	**Pre-treatment**	**Post-treatment**	**Statistics**	**Effect size**
Interview-based depression			*M* (*SD*)	*M* (*SD*)		
	PDI	267	41.13 (12.96)	34.08 (14.89)	$t(266) = 9.74$; $p < 0.001$	0.54
	PPS-A	271	42.12 (9.61)	34.90 (10.95)	$t(270) = 12.42$; $p < 0.001$	0.75
	PPS-S	270	26.75 (8.76)	23.26 (7.94)	$t(269) = 6.82$; $p < 0.001$	0.40
	NRS	276	7.02 (1.61)	5.72 (1.88)	$t(275) = 11.17$; $p < 0.001$	0.81
No interview-based depression		*N*	*M* (*SD*)	*M* (*SD*)		
	PDI	177	36.46 (13.74)	28.67 (14.53)	$t(176) = 9.52$; $p < 0.001$	0.57
	PPS-A	177	38.76 (8.90)	30.90 (10.44)	$t(176) = 10.16$; $p < 0.001$	0.88
	PPS-S	177	24.14 (9.01)	21.56 (8.24)	$t(176) = 4.72$; $p < 0.001$	0.29
	NRS	179	6.93 (1.79)	5.13 (1.90)	$t(178) = 11.78$; $p < 0.001$	1.01
CES-D depression		*N*	*M* (*SD*)	*M* (*SD*)		
	PDI	294	42.04 (12.55)	34.92 (14.64)	$t(293) = 10.57$;$p < 0.001$	0.57
	PPS-A	302	42.95 (8.75)	35.42 (10.64)	$t(301) = 12.94$; $p < 0.001$	0.86
	PPS-S	300	26.49 (8.74)	23.31 (7.82)	$t(299) = 6.73$; $p < 0.001$	0.36
	NRS	303	7.19 (1.61)	5.75 (1.91)	$t(302) = 12.57$; $p < 0.001$	0.89
No CES-D depression		*N*	*M* (*SD*)	*M* (*SD*)		
	PDI	147	33.51 (13.48)	25.98 (13.70)	$t(146) = 8.25$; $p < 0.001$	0.56
	PPS-A	143	36.30 (9.44)	29.16 (10.24)	$t(142) = 9.18$; $p < 0.001$	0.76
	PPS-S	144	24.26 (9.16)	21.14 (8.46)	$t(143) = 4.94$; $p < 0.001$	0.34
	NRS	149	6.57 (1.78)	4.99 (1.80)	$t(148) = 9.77$; $p < 0.001$	0.89

CES-D, centre for epidemiologic studies depression scale; PDI, pain disability index; PPS-A, pain perception scale affective; PPS-S, pain perception scale sensory; NRS, numeric rating scale; SD, standard deviation.

TABLE 4 | Results of the multilevel models evaluating interview-based depression (ICD-10) as predictor of pain outcomes.

	Estimate	SE	df	*t*	*p*
(1) Outcome: NRS					
Intercept	2.08	0.36	455	5.79	<0.001
Interview-based depression	0.55	0.17	455	3.32	0.001
NRS pre-treatment	0.44	0.05	455	9.11	<0.001
(2) Outcome: PDI					
Intercept	1.55	1.65	444	0.94	0.346
Interview-based depression	1.93	1.07	444	1.80	0.073
PDI pre-treatment	0.74	0.04	444	19.00	<0.001
(3) Outcome: PPS-A					
Intercept	7.43	1.92	448	3.87	<0.001
Interview-based depression	1.97	0.90	448	2.20	0.028
PPS-A pre-treatment	0.61	0.05	448	13.08	<0.001
(4) Outcome: PPS-S					
Intercept	9.29	1.00	447	9.33	<0.001
Interview-based depression	0.38	0.65	447	0.58	0.561
PPS-S pre-treatment	0.51	0.04	447	14.24	<0.001

NRS, numeric rating scale; PDI, pain disability index; PPS-A, pain perception scale affective; PPS-S, pain perception scale sensory; SE, standard error.

TABLE 5 | Results of the multilevel models evaluating questionnaire-based depression (CES-D) as predictor of pain outcomes.

	Estimate	SE	df	*t*	*p*
(1) Outcome: NRS					
Intercept	2.23	0.35	452	6.32	<0.001
CES-D depression	0.49	0.18	452	2.80	0.005
NRS pre-treatment	0.42	0.05	452	8.55	<0.001
(2) Outcome: PDI					
Intercept	1.58	1.61	441	0.98	0.329
CES-D depression	2.73	1.15	441	2.38	0.018
PDI pre-treatment	0.73	0.04	441	18.15	<0.001
(3) Outcome: PPS-A					
Intercept	8.03	1.91	445	4.21	<0.001
CES-D depression	2.39	0.98	445	2.44	0.015
PPS-A pre-treatment	0.58	0.05	445	12.10	<0.001
(4) Outcome: PPS-S					
Intercept	8.92	1.03	444	8.68	<0.001
CES-D depression	1.05	0.68	444	1.54	0.123
PPS-S pre-treatment	0.50	0.04	444	14.13	<0.001

CES-D, centre for epidemiologic studies depression scale; NRS, numeric rating scale; PDI, pain disability index; PPS-A, pain perception scale affective; PPS-S, pain perception scale sensory; SE, standard error.

depression or pain measurements. Previous studies investigating the association between depression and pain outcome either used the Symptoms Checklist-90-Revised (SCL-90-R) (Betrus et al., 1995; van der Hulst et al., 2008) the Beck Depression Inventory (BDI) (Kerns and Haythornthwaite, 1988; Glombiewski et al., 2010; Broderick et al., 2016), or the Depression Adjective Check List (DACL) (Kerns and Haythornthwaite, 1988). No comparable study investigating this topic used the CES-D. To assess pain, other studies used the multidimensional pain inventory (MPI) (van der Hulst et al., 2008; Broderick et al., 2016), the fear-avoidance beliefs questionnaire (FABQ2), the attribution of chronic pain patients inventory (KAUKON), the coping strategies and pain-related distress questionnaire (FESV) (Glombiewski et al., 2010), the pain rating index (PRI), or the West Haven-Yale Multidimensional Pain Inventory (WHYMPI) (Kerns and Haythornthwaite, 1988). Three studies applied pain intensity scales, like the Visual Analog Scale (VAS), and the PDI (Kerns and Haythornthwaite, 1988; van der Hulst et al., 2008; Glombiewski et al., 2010), which were applied in the current study, as well. Future research should therefore address the different impacts of different measurements more precisely.

Another reason for the incongruity in the results could be differences in the investigated study samples. The reported studies investigated chronic pain for hip and knee osteoarthritis (Broderick et al., 2016), low back pain (van der Hulst et al., 2008; Glombiewski et al., 2010), or female pain patients (Betrus

et al., 1995). The current study, on the other hand, investigated a heterogeneous sample of chronic pain patients. A heterogeneous sample of chronic pain patients was also investigated by Kerns and Haythornthwaite (1988) who found no association between questionnaire-based depression and pain treatment outcome. Moreover, the current sample exhibited a wide range of pain duration prior to the study. Hence, future studies should focus on pain type and duration.

As several studies in the past showed, pain catastrophizing is an associated variable in the relationship between pain and depression and may have a mediating role (Sullivan and D'Eon, 1990; Quartana et al., 2009). Due to this relation, Edwards et al. (2011) recommend to address both depression, catastrophizing, and pain experience in multimodal therapeutic programs. Moreover, another study reported an indirect relation between catastrophizing and depression via hope- and helplessness (Hülsebusch et al., 2016). Therefore, future studies should also consider potential mediating variables, like pain catastrophizing, hopelessness, and helplessness, when investigating the relationship between depression and pain outcome.

A main limitation of the study is its correlative design. Therefore, no causal inferences can be drawn and the internal validity of the results is rather low. There were several difference between the depressed and not depressed groups at baseline, which need to be considered as confounders. A randomized controlled trial assigning patients with or without depression to either multimodal pain management treatment or a control condition would have a higher internal validity. However, the study was conducted in routine care, which enhances the external validity of the results. Nevertheless, the results can solely be interpreted with regard to the applied measurements. The other main limitation is the heterogeneous sample size of the compared groups. As they arise from the results of the depression measurements the sample sizes were not influenceable as the study was not experimental.

Another limitation of the current study is that data were analyzed retrospectively. For more accurate conclusions, future studies should rather investigate this topic prospectively. Furthermore, the selection of the assessment methods of depression could be a limiting factor. The current study compared interview- and questionnaire-based measurements of depression. More precisely, we investigated semi-structured psychiatric interviews corresponding to the ICD-10 symptom checklist for mental disorders (Janca et al., 1994) and the German version of the Center for Epidemiologic Studies Depression Scale (Radloff, 1977). Although interview-based methods are recommended in general (Hooten, 2016), the Structured Clinical Interview (SCID) or the Composite International Diagnostic Interview (CIDI) are known as the gold standard in assessing depression (Spitzer et al., 1992; Wittchen, 1994; Haro et al., 2006; Eaton et al., 2007). Therefore, it is recommended for future research to use SCID or CIDI for interview-based assessment of depression.

Different self-report questionnaires to assess depressive symptoms have admittedly comparable sensitivity and specificity values (Hooten, 2016). However, scale-specific metrics of different depression questionnaires are heterogeneous (Wahl et al., 2014) and a meta-analytic review revealed variable effects of different measures (Burke et al., 2015). Thus, it is also recommended for future research to use more than one self-rate measurement for depression in order to compare results in one sample. As Burke et al. (2015) mention the CES-D and the BDI as the mostly used measurements of self-reported depressive symptoms, future research may for instance investigate these two questionnaires. Additionally, Poole et al. (2009) report the BDI to be a good screening method for depression in comparison with the WHO (five) Well Being Index (WBI-5) and the Hospital Anxiety and Depression Scale (HADS), Löwe et al. (2004) in turn show superiority of the PHQ-9. Therefore, the PHQ-9 could also be considered for future research.

Altogether, it would be reasonable to conduct a study in the future which compares several depression questionnaires, for example BDI, CES-D, and PHQ-9, and several clinical interviews based on ICD-10 as well as DSM 5, like SCID or CIDI, within one investigation.

Future studies could also assess the construct of depression more differentiated. Blatt (2004) identified a difference in the development and appearance of two subtypes of depression, the anaclitic and the introjective depression. Addressing the differences of these subtypes, the Anaclitic-Introjective Depression Assessment (AIDA) was developed (Rost et al., 2018). Applying AIDA might prove fruitful in further studies on depression as predictor of pain treatment outcome.

Not having gathered confounding variables could also have a limiting effect in the current study. As a meta-analysis of Burke et al. (2015) revealed anxiety to have a larger impairing effect on pain outcome than depression, future studies should consider anxiety, as well.

The comprehensive assessment of pain, however, can be seen as a strength of the present study.

CONCLUSION

The way depression was operationalized did not influence whether depression predicts pain outcomes or not.

DATA AVAILABILITY

Data regarding this study will not be shared, because clinical data was investigated and we made an agreement with the clinic for not to publish participant data, but only analyses and interpretations.

ETHICS STATEMENT

This study was conducted in accordance with the Declaration of Helsinki and ethical laws were applied. All participants signed a consensus declaration and agreed to the analysis of their anonymous data.

AUTHOR CONTRIBUTIONS

SF: drafting the work, substantial contributions to the conception and design of the work, analysis and interpretation of data for the work, final approval of the version to be published, and accountability for all aspects of the work. CL: revising and final approval of the work, substantial contributions to the acquisition of data for the work, and accountability for all aspects of the work. TO: language and final approval, revising the work, interpretation of data, and accountability for all aspects of the work. TP: revising the work critically for important intellectual content, substantial contributions to analysis and interpretation of data for the work, final approval of the version to be published, and accountability for all aspects of the work. CP: revising the work critically for important intellectual content, substantial contributions to the acquisition of data for the work, final approval of the version to be published, and accountability for all aspects of the work.

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Expressive Suppression and Negative Affect, Pathways of Emotional Dysregulation in Psoriasis Patients

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The main goal of this study was to assess the emotion regulation (ER) mechanisms, such as expressive suppression and cognitive reappraisal, in patients with psoriasis, as compared with healthy persons not afflicted by dermatological diseases. Moreover, the study intended to carry on a multidimensional assessment of emotional mechanisms in persons with psoriasis, highlighting the differences between psoriasis patients and healthy participants, in order to identify the specific patterns of emotion dysregulation (ED) in psoriasis. Another goal of the study was to investigate the predictors of ED among different emotional patterns. We presumed that the maladaptive ER mechanisms are higher in psoriasis patients than in the control group and there are specific dysregulation patterns in psoriasis patients as negative emotions tendency. This cross-sectional study was performed on 192 individuals aged between 35 and 75 years (mean age 59). The sample was divided in two groups: the clinical group including 91 patients with a diagnosis of psoriasis vulgaris and the control group including 101 healthy persons. The results of the present study suggest that psoriasis patients more frequently used emotional suppression – a maladaptive ER mechanism – as well as ED patterns – i.e., impulse control difficulties, and nonacceptance of emotional responses. They also displayed trait tendency to a negative emotional response. In fact, in people with psoriasis, the presence of suppression mechanism and negative affect of trait could predict that 35% of patients will show emotional dysregulated patterns, while living with higher levels of ED. The results of our study are important in the clinical practice, helping clinicians to better understand the emotional vulnerability of people that live with psoriatic disease, and to optimize the disease management and patient care in an interdisciplinary approach.

Keywords: expressive suppression, negative affect, emotion dysregulation, psoriasis, maladaptive mechanisms

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INTRODUCTION

Psoriasis is a chronic, visible, immune-mediated psychocutaneous disease, which can impact considerably the patient's life quality and their daily functioning (Yadav et al., 2013; França et al., 2017). This skin condition is characterized by circumscribed, erythematous, dry, scaly plaques and has a fluctuating severity over time (Reich, 2012; Brandon et al., 2019).

A range of co-morbidities is associated with psoriasis, including cardiovascular disease, diabetes, obesity, metabolic syndrome, and common psychological disorders like depression and anxiety (Picardi et al., 2004; Gisondi et al., 2013; Miller et al., 2013; Lakshmy et al., 2015; Linder et al., 2015).

Several studies have been conducted showing that there is a significant relationship between psychological stress and psoriasis, highlighting that the stress impact may be higher in psoriasis patients compared to other skin conditions (Basavaraj et al., 2011; Rieder and Tausk, 2012; Nelson et al., 2013). There is evidence in the literature showing that psychological stress may have a role in the onset or exacerbation of a variety of skin diseases (Al'Abadie et al., 1994). Devrimci-Ozguven et al. (2002) suggests that stressful incidents occur before the onset of psoriasis flares in approximately 68% of adult patients.

Although the existence of a relationship between stress and the exacerbation of diffuse plaque psoriasis is now well known, the studies on the specific emotional mechanisms are still at the beginning.

There are different conceptualizations of ER/ED. The starting point of view is that ER refers to attempts individuals make to influence which emotions they have, when they have them, and how these emotions are experienced and expressed (Sloan and Kring, 2007). ER involves the pursuit of desired emotional states (i.e., emotional goals) in the service of superordinate motives (Tamir, 2016). A recent definition (Bunford et al., 2015) considers ER as an individual's ability to modulate: the speed with which and what degree to which the physiological, experiential, and behavioral expression of an emotion escalates, the intensity of physiological, experiential, and behavioral expression of an emotion, and the speed with which and degree to which physiological, experiential, and behavioral expression of an emotion deescalates in a manner congruent with an optimal level of functioning.

In opposition to the definition of ER, Werner and Gross (2010) define ED as "the inability to flexibly respond to and manage emotions." There are a wide variety of approaches used in the research of the complex phenomena included under the heading of ED. Gratz and Roemer (2004) conceptualized ED as a process that involves four dimensions: awareness and understanding of own emotions, acceptance of own emotions, ability to control impulsive behaviors when leaving negative emotions, and capability to use appropriate ER strategies to achieve desired goals. Based on this conceptualization, the authors defined ED (or the difficulties in ER) as the relative absence of any or all of these abilities, and developed a model of ED in six factors, that we used in the present research. The six ED factors were assessed as the DERS's six subscales (Difficulties in Emotion Regulation Scale).

In the present work, we used Gross' conceptual framework of ER who considers the temporal aspects of emotion. In this conceptualization, emotion is a special case of affect, relatively brief and referential (Frijda, 1986; Ekman, 1992). Gross (1998) in describing the ER process model makes the distinction between antecedent- focused (e.g., cognitive reappraisal) and response-focused (e.g., expressive suppression) ER. Antecedent-focused regulation consists of early attempts to modify emotions that occur before the full activation of emotional response. Response-focused regulation consists of late attempts to modify emotion, when the emotional response has already generated. Cognitive reappraisal refers to thinking about a situation in a manner that can alter its emotional response. Expressive suppression occurs when an individual attempts to inhibit the behavior of emotional expression (Gross, 1998).

The aim of this study was to assess the ER mechanisms such as expressive suppression and cognitive reappraisal in patients with psoriasis as compared with healthy persons not afflicted by dermatological diseases. Moreover, the study intended to carry on a multidimensional assessment of emotional mechanisms in persons with psoriasis, highlighting the differences between psoriasis patients and healthy participants, to identify the specific patterns of ED in psoriasis. Following this purpose, different conceptualization of emotion and ER were considered, assessing the type (trait/state) and quality (positive/negative) of emotion (PANAS model known as consensual model), the adaptive/maladaptive ER mechanisms (Gross and John two-factor model), and the ED patterns when living negative emotions (Gratz and Roemer's six-factor model).

The present research is going to answer whether or not the adaptive and maladaptive ED mechanisms like expressive suppression and cognitive reappraisal in psoriasis patients differ from that of a healthy person. The aim of the study is also to investigate the predictors of ED (among different patterns of the emotional phenomenon). We presume that there are specific dysregulation patterns in psoriasis patients, and the maladaptive ER mechanisms are higher in psoriasis patients than in the control group. We presume also that the difficulties in ER depend not only on the type (trait/state) and quality (positive/negative) of emotion but also on the maladaptive strategies (expressive suppression). In psoriasis patients, the contribution of expressive suppression in ED is higher than in healthy persons. Expressive suppression and cognitive reappraisal in patients with dermatological diseases have never been investigated so far, especially in the context of a multidimensional assessment of the emotional phenomenon.

MATERIALS AND METHODS

Sample

This cross-sectional study was performed on 192 individuals aged between 35 and 75 years (mean age 59). The sample was divided in two groups: the clinical group including 91 patients with a diagnosis of psoriasis vulgaris, and the control group, consisting of 101 healthy volunteers. The study was conducted in the Dermatology and Venereology Clinic, of the "SS Annunziata" University Hospital in Chieti, Italy between October 2017 and January 2019 in accordance with ethical standards on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

The patients came in the clinic for an out-patient visit and completed the assessment protocol in the presence of a clinical psychologist with experience in emotion assessment, who was blind regarding the disease severity. The severity of the psoriasis

was assessed by a dermatologist. Psoriasis vulgaris was the only type of psoriasis that was considered for the study. All the individuals signed the informed consent form and a questionnaire regarding their demographic data. The diseases characteristics such as illness length, illness severity, and type of medication are presented in **Table 1**.

Inclusion criteria were as follows: age (over 18) and the diagnosis of psoriasis vulgaris. Exclusion criteria were as follows: history of a major neurological disease (dementia – 1) or a major psychiatric condition (anxiety – 2, depression – 1), and the inability to complete the assessment for different reasons (age, culture, education – 3), failure to give informed consent (2).

The control group of healthy participants was matched to the patients by gender, age, and educational qualification, did not present any somatic or psychic disease, and all signed an agreement to participate in this study. The demographical characteristics of the participants are presented in **Table 2**.

Measures

Illness Severity Assessment

Psoriasis Area Severity Index

Psoriasis Area Severity Index (PASI) was used to establish severity of psoriasis. The human body is divided into four areas separately: head (H) (10% of a person's skin); arm (A) (20%); trunk (T) (30%); and legs (L) (40%). The four scores are combined into the final PASI score. Also, within each body area, the severity is estimated by three clinical signs: erythema (redness), induration (thickness), and desquamation (scaling). Severity is evaluated on a scale of 0 (none) to 4 (maximum).

The sum of all three severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by the weight of the respective section. A PASI score < 10 depicts a mild psoriasis while when PASI score is >10 psoriasis is moderate to severe (Augustin et al., 2018). The mean PASI score in our clinical group was 7.62 (SD 8.93).

Dermatological Quality Severity Index

Dermatological Quality Severity index (DLQI) designed to measure the health-related quality of life of patients older than 16 suffering from a skin disease. DLQI consists of 10 questions concerning a dermatology patient's perception of the impact of their skin disease on different aspects of their quality of life (QoL) over the last week, including symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment. Higher scores indicate greater impairment of QoL. The mean DLQI score in our clinical group was 6.06 (SD 5.62).

Psychological Assessment

All patients were asked to complete the following psychological variables: expressive suppression, cognitive reappraisal, ED and its components, positive and negative affect of state, and positive and negative affect of trait. The research protocol included Italian validated versions of several questionnaires: Emotion Regulation Questionnaire (ERQ), Difficulties in Emotion Regulation Scale (DERS, Positive and Negative Affect Schedule of Trait (PANAS of Trait), and Positive and Negative Affect Schedule of State (PANAS of State).

Emotion Regulation Questionnaire

Emotion Regulation Questionnaire (ERQ; Gross and John, 2003) was used to measure ER. The ERQ is a 10-item checklist divided into two sub-scales, capturing two commonly used ER strategies, cognitive reappraisal and expressive suppression. Reappraisal refers to thinking differently about a potential stressor event, to manage better the emotional response, whereas suppression refers to diminishing or inhibiting the emotional expression when facing the same emotional event. Participants were required to rate their response on a 7-point Liker-type scale (1 = totally disagree to 7 = totally agree) on their usual ways of emotional regulation. A higher score indicates a higher tendency to adopt one or another strategy. The total score on

TABLE 1 | Disease characteristics in psoriasis group: illness length, illness severity, and type of medication.

Illness length, % (*n*)	
≤1 year	5.8 (5)
≤5 years	7.4 (8)
≥5 years	86.8 (79)
Illness severity, % (*n*)	
PASI < 10	82.6 (75)
PASI ≥ 10	17.4 (16)
DLQI < 10	79.2 (72)
DLQI ≥ 10	20.8 (19)
Medication, % (*n*)	
Biological	(12.1) 11
Phototherapy	(19.7) 18
Topical	(44.1) 41
No medication, % (*n*)	(24.1) 21

TABLE 2 | Participants characteristics.

	N	Age in years	Gender	Working status	Civil status	Education (years)
		Mean ± SD	Female *n* (%)	Working *n* (%)	Married *n* (%)	Mean ± SD
Psoriasis	91	49.17 ± 16.54	46 (50.7)	51 (58.2)	61 (67.3)	11.56 ± 2.91
Healthy individuals	101	50.82 ± 10.84	53 (52.3)	62 (62.4)	73 (72.2)	12.48 ± 3.84
Total sample	192	50.08 ± 16.67	99 (58.2)	113 (59.2)	134 (69.4)	12.86 ± 3.92

ERQ indicates the global value of ER. The internal consistency in the present sample was 0.73 for expressive suppression and 0.79 for cognitive reappraisal.

Difficulties in Emotion Regulation Scale

Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004) is a 36-item multidimensional self-report measure, subdivided into six subscales: (1) *Nonacceptance* of emotional responses; (2) *Goals* (difficulties engaging in goal-directed behavior when experiencing negative emotions); (3) *Impulse* (impulse control difficulties when experiencing negative emotions); (4) *Awareness* (lack of emotional *awareness)*; (5) *Strategies* (limited access to ER *strategies* that are perceived as effective); and (6) *Clarity* (lack of emotional clarity), assessing the individual's characteristic patterns of ED. Items are rated on a 5-point Likert-type scale (from 1 = almost never to 5 = almost always). A high score indicates the presence of a major difficulty in ER. The total score on DERS indicates a global value of ED. A high total score indicates a high level of ED. In the current sample internal consistency ranged between 0.73 for awareness and 0.81 for strategies and acceptance.

Positive and Negative Affect Schedule

Positive and Negative Affect Schedule (PANAS; Watson et al., 1988) is a 20-item questionnaire. Ten items measure positive affect (interested, excited, and inspired), and 10 items measure negative affect (e.g., upset, afraid). PANAS was designed to measure affect in various contexts such as at the present moment, the past day, week, or year, or in general (on average). Thus, the scale can be used to measure state affect, dispositional or trait affect, emotional fluctuations throughout specific period, or emotional responses to events. High scores are related to the more frequent use of one kind of emotion.

In the present study, we used two versions of PANAS: PANAS trait, evaluating the emotions that one generally proves (trait tendency to experience positive or negative emotions), and PANAS state, evaluating the emotions that one proves in the evaluation moment (positive or negative emotional reactivity in a specific situation). Results were recorded as: positive affect of trait (PAT), negative affect of trait (NAT), positive affect of state (PAS), and negative affect of state (NAS). The Cronbach's α in the present sample ranged between 0.79 for PAS and 0.86 for NAS.

Statistical Analysis

Data were entered into a computerized database and analyzed with the SPSS Statistics version 21 (IBM) program. The level of significance was set at $p < 0.05$ and $p < 0.001$. Descriptive analyses were run to determine means, standard deviations, and ranges for all characteristics of both psoriasis and control participants. All variables were checked for the assumption of normal distribution. Bivariate correlations were performed to determine relations between Suppression, Reappraisal, DERS scores, Positive and Negative Affect of Trait, and Positive and Negative Affect of State. In order to verify our hypothesis about differences in mean results between patients with psoriasis and healthy persons in ER mechanisms, the independent samples *t*-test was performed. Standard multiple regression was applied to predict ED from the expressive suppression, negative affect of trait, and negative affect of state, separately for psoriasis patients and healthy individuals. The dependent variable was ED (DERS total score). The independent variables were expressive suppression, negative affect of trait, and negative affect of state.

RESULTS

Emotion Regulation Mechanisms in Psoriasis and Healthy Individuals

Our results suggest that psoriasis patients show a higher maladaptive mechanism (expressive suppression) when attempting to regulate their emotions ($Z = 3.112$, $p < 0.002$) compared to healthy controls, where no difference was shown in the adaptive mechanism (cognitive reappraisal) (**Table 3**).

As for the maladaptive regulation, we conclude that patients with psoriasis show major ED patterns as opposed to healthy controls and reported higher scores on two out of six dimensions of DERS: nonacceptance ($Z = 2.311$, $p = 0.022$) and impulse ($Z = 3.193$, $p = 0.002$) (**Table 3**).

The PANAS score was consistently higher for psoriasis patients, compared to normal subjects on only one-dimension NAT (negative affect of trait). There was no difference between the two groups regarding negative or positive affect of state and positive affect of trait (**Table 3**).

To better delineate the relation between disease severity and the mechanism of ED, we performed a statistical analysis dichotomizing patients into two groups (PASI ≥ 10 and PASI < 10). We found no differences between the two groups.

Correlations Between Variables

When we tried to correlate ED and positive and negative affect in psoriasis patients, we found that negative affect of trait was strongly related with ED (0.472, $p < 0.001$, while negative affect of state was only moderately correlated (0.27, $p < 0.05$). DERS also correlated with suppression mechanism of emotion control (0.28, $p < 0.001$). Moderate correlation was found between DERS and disease severity (0.37, $p < 0.05$). Quality of life negatively correlated in psoriasis patients with positive affect of trait (−0.47, $p < 0.001$) (**Table 4**).

In healthy controls, there was a positive moderate correlation between suppression and DERS (0.235, $p < 0.05$) and DERS resulted negatively correlated with positive affect of trait (−0.29, $p < 0.001$), and positively related with negative affect of trait (0.37, $p < 0.001$) (**Table 5**).

There were no significant correlations between DERS and all other variables (e.g., age and gender) in both study groups.

Predictors of the Emotion Dysregulation in Psoriasis and Healthy Group

In order to investigate the ED's predictors (among ER mechanisms, quality, and type of emotions), a multiple linear regression was

TABLE 3 | Emotion assessment in the two groups (psoriasis patients and controls).

	Psoriasis	Controls		
	(*n* = 91)	(*n* = 101)		
	Mean ± SD	Mean ± SD	*t*	*p*
Emotion regulation mechanisms				
Expressive suppression	17.49 ± 5.95	14.70 ± 5.85	3.112	0.002**
Cognitive reappraisal	29.71 ± 7.67	30.37 ± 6.76	–0.624	0.533
Emotion regulation	47.09 ± 10.56	45.16 ± 8.65	1.374	0.171
Emotion dysregulation				
Nonacceptance	13.41 ± 6.65	11.39 ± 5.14	2.311	0.022*
Goals	12.41 ± 5.14	12.01 ± 4.02	0.585	0.559
Impulse	12.47 ± 5.15	10.30 ± 4.02	3.193	0.002**
Awareness	6.81 ± 3.20	7.41 ± 3.12	1.255	0.211
Strategies	17.21 ± 5.78	17.16 ± 5.05	0.064	0.949
Clarity	10.44 ± 4.76	9.75 ± 3.18	1.169	0.244
Emotion dysregulation	72.79 ± 23.55	68.01 ± 16.46	1.608	0.110
Affect quality				
Positive affect of trait	33.74 ± 7.45	31.49 ± 7.74	1.975	0.052
Negative affect of trait	21.16 ± 9.23	17.65 ± 6.64	2.970	0.003**
Positive affect of state	30.01 ± 8.21	29.11 ± 7.91	0.748	0.456
Negative affect of state	14.62 ± 7.31	15.14 ± 5.38	–0.548	0.585

*Differences between groups. *p < 0.05; **p < 0.005.*

TABLE 4 | Correlations between variables in psoriasis group: S (expressive suppression), R (cognitive reappraisal), ER (emotion regulation measured as total score of ERQ), PAT (positive affect of trait), NAT (negative affect of trait), PAS (positive affect of state), NAS (negative affect of state), ED (emotion regulation measured as total score of DERS), AGE, TIME (illness length), PASI (disease severity), and DLQI (quality of life). The relevant values are presented in bold format.

	1	2	3	4	5	6	7	8	9	10	11
1. ED	–										
2. AGE	–0.015	–									
3. S	**0.312****	–0.026	–								
4. R	0.011	0.009	–0.169	–							
5. ER	0.185	0.004	0.685**	0.828**	–						
6. PAT	–0.193	–0.038	–0.072	**0.338****	0.205	–					
7. NAT	**0.497****	–0.154	–0.017	–0.137	–0.111	**0.217***	–				
8. PAS	–0.074	0.066	0.143	0.080	–0.039	0.688**	0.296**	–			
9. NAS	**0.300****	–0.153	–0.017	–0.092	–0.078	0.010	0.669**	0.056	–		
10. DLQI	0.167	–0.233	–0.104	–0.209	–0.204	**–0.464****	–0.140	–0.220	0.076	–	
11. PASI	0.347	–0.168	0.086	–0.045	0.011	–0.069	0.056	0.117	0.138	0.504**	–
12. TIME	0.145	**0.540***	–0.224	0.044	–0.093	0.132	0.333	0.062	0.204	–0.226	–0.12

**p < 0.05; **p < 0.01 (two-tailed).*

run, considering ED as dependent variable, and expressive suppression, negative affect of trait, and negative affect of state as independent variables. Results of the multiple regression in psoriasis group suggest that these variables statistically significantly predicted ED, $F(3, 89) = 13{,}860$, $p < 0.0005$, $R^2 = 0.35$, which indicates that 35% of ED variance is explained by our model. Inspection of the regression coefficients indicates that only two variables of three are significant predictors of level of ED in psoriasis: expressive suppression ($\beta = 0.304$, $p < 0.001$) and negative affect of trait ($\beta = 0.557$, $p < 0.001$) (**Table 6**).

Psoriasis patients with the tendency to negatively respond to emotional stressors and who control their emotions by not expressing it, especially by suppressing the behavioral expression are more likely to present a higher level of ED, than patients who do not use these mechanisms.

In healthy controls, these variables statistically significantly predicted ED, $F(3, 97) = 8{,}146$, $p < 0.0005$, $R^2 = 0.19$, which indicates that only 19% of ED variance is explained by the model. Inspection of the regression coefficients indicates that the same two variables of three are significant predictors of level of ED in healthy persons: expressive suppression ($\beta = 0.230$, $p < 0.05$), and negative affect of trait ($\beta = 0.441$, $p < 0.001$).

The results suggest that negative affect of trait is the strongest predictor of ED both in psoriasis and control group, followed by expressive suppression. There are two important differences between the two groups regarding the prediction model of ED: the model explains the higher ED variance in psoriasis patients (35%) when compared to healthy persons (19%), and the contribution of expressive suppression is moderately

TABLE 5 | Correlations between variables in control group: S (expressive suppression), R (cognitive reappraisal), ER (emotion regulation measured as total score of ERQ), PAT (positive affect of trait), NAT (negative affect of trait), PAS (positive affect of state), NAS (negative affect of state), ED (emotion dysregulation measured as total score of DERS), and AGE. The relevant values are presented in bold format.

	1	2	3	4	5	6	7	8
1. ED	–							
2. AGE	0.129	–						
3. S	**0.235***	0.082	–					
4. R	–0.129	0.048	–0.065	–				
5. ER	0.058	0.093	0.626**	0.738**	–			
6. PAT	**–0.291****	–0.161	–0.123	**0.237***	0.102	–		
7. NAT	**0.377****	–0.182	0.019	–0.156	–0.110	0.096	–	
8. PAS	**–**0.083	0.035	–0.071	**0.388****	**0.255****	0.756**	0.043	–
9. NAS	0.177	0.017	0.035	–0.068	–0.029	0.031	0.629**	0.172

*$p < 0.05$; **$p < 0.01$ (two-tailed).

TABLE 6 | Standard regression analysis summary for psoriasis patients' variables predicting emotion dysregulation.

Variables	*B*	SEB	β
Expressive suppression	1.169	0.352	0.304**
Negative affect of trait	1.391	0.309	0.557**
Negative affect of state	–0.216	0.389	–0.069

$R^2 = 0.35$ ($N = 89$, $p < 0.001$). **$p < 0.001$.

TABLE 7 | Standard regression analysis summary for healthy individuals' variables predicting emotion dysregulation.

Variables	*B*	SEB	β
Expressive suppression	0.648	0.256	0.230*
Negative affect of trait	1.093	0.290	0.441**
Negative affect of state	–0.331	0.358	–0.108

$R^2 = 0.19$ ($N = 101$, $p < 0.001$). *$p < 0.05$; **$p < 0.001$.

significant in healthy persons ($p < 0.05$), and quite significant in psoriasis patients ($p < 0.001$) (**Table 7**).

DISCUSSION

ER, the experiencing, processing, and modulating of emotional responses, is necessary to manage the emotional stressors common in patients with chronic illness. The present research intended to realize a multidimensional assessment (adaptive and maladaptive emotional mechanisms, ED and its components, quality and type of affect) in subjects affected by psoriasis, highlighting the differences with healthy controls. The study tried to investigate different emotional mechanisms that could better reflect both psychosomatic and somatopsychic perspective on the emotional impact in chronical illness.

The studies on the ER in chronical illness are still at the beginning and scarce in number. Among these studies, only a few are assessing the role of expressive suppression and cognitive reappraisal mechanisms (Wierenga et al., 2017). As far as we know, the present study is the first to investigate, in a multidimensional assessment, the expressive suppression mechanism in psoriasis.

Our study revealed that patients with psoriasis significantly differ from healthy individuals in expressive suppression, negative affect of trait, nonacceptance of own emotions, and in difficulties in controlling their impulses. There is no difference between the two groups in the use of adaptive ER mechanisms. People with psoriasis use more frequently a maladaptive regulation mechanism, trying to modify their emotion, aiming to suppress the behavior of emotional expression.

Regarding the quality of emotions, our study suggests that the difference between psoriasis patients and healthy controls is more pronounced as for negative emotions of trait meaning that psoriatic patients experience more frequently negative emotions. The existing literature supports the presumption that higher negative affect in psoriasis patients could be relate to higher expressive suppression. John and Gross (2004) suggests that "re-appraisers" experience and express greater positive emotion and lesser negative emotion, whereas "suppressors" experience and express lesser positive emotion, yet experiencing greater negative emotions.

Cognitive reappraisal and expressive suppression are two emotional regulation mechanisms that directly influence the physiologic body response (e.g., reappraisal decreases the cardiac pressure. Suppression is a maladaptive emotional regulation mechanism which has been shown to produce sympathetic activation, and may substitute an appropriate control by increasing the emotional arousal. Literature suggests that the biological mechanism of suppression and stress have common components, such as cortisol release (Gross and Levenson, 1993, 1997). At the same time, acute psychologic stress is associated with increased glucocorticoid levels, adversely affecting skin barrier function recovery, induced by tape stripping (Lams et al., 2009). This induced barrier alteration function could explain the stress impact in onset, development, exacerbation of psoriatic plaques in persons affected by psoriasis.

In line with previous researches, our study suggests the existence of higher ED patterns in patients with psoriasis (Ciuluvica et al., 2014; Innamorati et al., 2016; Almeida et al., 2017). Patients reported more problems than healthy controls with the acceptance of emotions, and in

controlling their impulses when experiencing negative emotions. Patients with more severe disease cases are more likely to show a dysregulated emotional mechanism.

The results verified the hypothesized model of prediction of ED. In psoriatic patients, the presence of a suppression mechanism and negative affect of trait (the trait tendency of emotional response) could predict that 35% of patients will show emotion dysregulated patterns, experiencing higher levels of emotional dysregulation. There are different results in the healthy controls model because, as our results suggest, the ED is predicted only in 20% by the model. Suppression is only a highly significant predictor of ED in psoriasis patients. In healthy individuals, the significance of suppression as predictor of ED is moderate.

The results suggest that there are emotional patterns in psoriasis patients (expressive suppression, tendency to experience more negative emotions, nonacceptance of own emotions) that may lead to an increase of negative affectivity, forcing patients to supplement their efforts in managing the negative emotional arousal that impacts the wellbeing and life quality.

Indeed, the results of our study also suggest that quality of life in psoriatic patients is significantly correlated with negative affectivity. However, at this point of the study, we are not able to conclude the decisive role of ER in the etiology of psoriasis, but our results suggest the existence of an emotional vulnerability in people affected by psoriasis. Negative emotions that last too long, excessive suppression of emotions, especially when paired with lack of behavioral expression can, through the vegetative nervous system, deregulate the hormonal and immunological systems, cause somatic dysfunction, and finally lead to disease or aggravate the disease course.

The results of the present study suggest that psoriasis patients used a maladaptive ER mechanism (emotional suppression) more frequently, experienced more negative emotions of trait (trait tendency to a negative emotional response), and use emotional dysregulation patterns more frequently: impulse control difficulties, and nonacceptance of emotional responses. The relationship between these specific emotional patterns, the diseases particularities, and their implication in the disease control should be analyzed in more detail in future research because these findings could help physicians to better manage the disease with regard to QoL.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

This manuscript updates and extends a preliminary research report presented at the 6th Annual Scientific Conference of the European Association of Psychosomatic Medicine (EAPM) 2018. The final version of this manuscript was written by CC, PA, and MF. CC and PA contributed to the collection and analysis of psychological and medical data and wrote a preliminary version of this manuscript.

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BRIEF RESEARCH REPORT
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A Pilot Study of the Relationship Between Pregnancy and Autoimmune Disease: Exploring the Mother's Psychological Process

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Autoimmune disease mainly affects women in their reproductive years and has a significant impact on childbearing. Pregnancy can induce an improvement of the mother's symptomatology in some diseases such as rheumatoid arthritis while exacerbating or having no effect on other autoimmune diseases as multiple sclerosis (Borchers et al., 2010). This uncertainty can affect the process of psychological reorganization, which leads to the achievement of a maternal identity. The quality of the mother-fetus emotional bond is considered particularly relevant for the subsequent attachment relationship and the psychological development of the infant (Ammaniti et al., 2013). In the last trimester of pregnancy, 15 women with different autoimmune diseases were interviewed using the IRMAG-R (Ammaniti and Tambelli, 2010). They also completed a battery comprising: PAI (Della Vedova et al., 2008); MAAS (Busonera et al., 2016); DAS (Gentili et al., 2002); PBI (Scinto et al., 1999); MSPSS (Prezza and Principato, 2002); DERS, (Giromini et al., 2012); CES-D (Fava, 1983); HCR-TS (Bova et al., 2012). All interviews were audiotaped, transcribed verbatim, and analyzed by Atlas.ti. The results show that women with autoimmune disease were ambivalent toward pregnancy, had high levels of depression, had difficulties in recognizing physical and psychological changes, and had difficulties in imagining the child. These are considered risk factors that could negatively affect the postnatal mother-infant relationship. These results focus on the importance of early multidisciplinary interventions that can support expectant women when they show signs of relationship difficulties with their infants prior to his/her birth.

Keywords: risk pregnancy, autoimmune disease, prenatal attachment, maternal representations, qualitative and quantitative analysis

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INTRODUCTION

Autoimmune diseases are chronic multi-system disorders characterized by organ and tissue damage caused by self-reactivity of different effectors mechanisms of the immune system, specifically antibodies and T cells. Predisposition to these diseases has been related to genetic, epigenetic, and environmental factors. Thus, autoimmune diseases mostly affect women and frequently occur

during reproductive years and have implications for fertility and pregnancy (Tabarkiewicz et al., 2018). Successful pregnancy depends on early changes in the mother, which rely on modifications of the innate and adaptative immune system, inducing tolerance to the semi-allogenic fetus (Carvalheiras et al., 2012). Nevertheless, if pregnancy is planned during periods of inactive or stable disorder, the result often is giving birth to healthy full-term babies. Nonetheless, pregnancies in most autoimmune diseases are still classified as high risk because the pregnancy may have an influence on autoimmune disorder improvement or worsening and the autoimmunity increases miscarriage risks and, perinatal mortality (Borchers et al., 2010; Vengetesh et al., 2015).

Becoming a mother is one of the most central transitions in life, which requires restructuring goals, behaviors, and responsibilities to achieve a new conception of self (Kaiser et al., 2009). This transition is qualitatively influenced by her conscious and unconscious responses to it. These can be considered as biological, psychological, and psychosocial. Especially pertinent are her age, socioeconomic status, kind of autoimmune disease, and circumstances of the current pregnancy. Mental health problems such as depression and anxiety are common among people with autoimmune diseases (Boeschoten et al., 2017; Marchini et al., 2018). Autoimmune diseases, such as multiple sclerosis, can affect adjustment at both the individual and couple level. Couples facing multiple sclerosis have reported lower rates of relationship satisfaction than healthy controls (Crangle and Hart, 2017). Social support has been recognized as a protective factor for concern about maternal depressive symptoms (Harrison and Stuifbergen, 2002), predicting greater role participation, and satisfaction in mothers with multiple sclerosis (Farber et al., 2015). Trust and perceived support also are necessary for building a good patient-health care provider relationship (Bova et al., 2012). The literature shows a paucity of qualitative studies that consider the maternal experiences of women with autoimmune diseases. The focus of this issue is frequently presented from a medicalized perspective, often conducted by medical or health professionals and aimed at other professionals on how to support parents (Farber, 2000).

The woman with an autoimmune chronic disease who becomes pregnant might be more psychologically adjusted to her condition but still have fears that the pregnancy will exacerbate her disease in addition to worrying that her condition could potentially harm her baby. The occurrence of a medical illness in the expectant mother increases the complexity of her care, and it can also interfere with the woman's ability to cope with the pregnancy and to comply adequately with the medical needs of her condition (Zager, 2009; Rasmussen et al., 2013). The increased stress experienced in high-risk pregnancies might affect the construction of the prenatal attachment (Bulbul et al., 2018). Attachment starts when a woman responds positively to pregnancy. It is known that the mother-infant relationship in the postpartum period is strongly related to the prenatal attachment (Ammaniti et al., 2013; Cataudella et al., 2016a,b).

Ehrlich (2019) argues that attachment likely plays a role in shaping immune processes. Some theoretical models underline the importance of social experiences that take place early in development that might serve as "programming" factors for the immune system. Other researchers have highlighted how ongoing social experiences in adulthood such as conflict in close relationships and ongoing stress might shape immune processes (Miller et al., 2009; Fagundes et al., 2013).

These premises underline the need for attention to factors that can positively or negatively affect the transition to motherhood for women with autoimmune diseases. The central aim of our pilot study was to explore psychological dynamics during pregnancy as well as the possibility of evidencing vulnerabilities and risk factors that could negatively interfere with the establishment of a bond between a mother and her baby.

METHODS

Participants

Fifteen Italian women were contacted during their follow-up visits to the Department of Prenatal Diagnosis and Fetal Therapy "Ospedale Microcitemico" in Cagliari (Italy). They have a mean age of 36.4 years (SD = 5.4); their mean gestational age was 29.6 weeks (SD = 5.6).

Sociodemographic characteristics and pregnancy-related variables are reported in **Table 1**.

Procedure

All expectant women were contacted and interviewed by psychologists skilled in administering all investigation instruments. The presence of autoimmune disease constituted the inclusion criteria in the study. All pregnant women voluntarily accepted to participate in the research; they signed the format of informed consent and were interviewed. Then, they completed some self-report questionnaires, fulfilled between the second and third trimester of pregnancy. The study is still ongoing, and it includes a follow-up 3 months after birth. In this paper we illustrate the results of the sample at T1 (during pregnancy).

The study was accepted by the Ethics Committee at the University of Cagliari - Italy (referring to the Department of Pedagogy, Psychology, Philosophy).

Measures

Questionnaire on Sociodemographic Characteristics and Pregnancy Related Variables

This questionnaire is devised *ad hoc* to collect some relevant information (e.g., age, educational level, gestational age, parity, pregnancy planning, marital status, type of autoimmune disease and, time of diagnosis).

Interview of Maternal Representations During Pregnancy-Revised Version (IRMAG-R; Ammaniti and Tambelli, 2010)

This interview was characterized by 41 questions; they assessed in detail the effect of traumatic past and/or recent experiences, furthermore the occurrence of mother's preoccupations and/or disproportionate fears regarding the woman or the baby.

TABLE 1 | Sociodemographic characteristics and pregnancy-related variables.

Variable	Frequency
Age group	
28–35 years	7
36–46 years	8
Educational level	
Middle school	1
High school	2
University degree	9
Postgraduate	3
Marital status	
Married	12
Cohabiting	2
Engaged	1
Parity	
Primiparae	9
Multiparae	6
Previous miscarriage(s)	
Yes	5
No	10
Pregnancy planning	
Planned	11
Unplanned	4
Sex of the baby	
Male	6
Female	8
Missing	1
Types of autoimmune diseases	
Mixed connective tissue diseases	1
Atopic dermatitis	1
Type 1 diabetes	2
Psoriasis	1
Autoimmune thyroiditis	5
Systemic lupus erythematosus	1
Multiple sclerosis	2
Autoimmune thyroiditis + Type 1 diabetes	1
Autoimmune thyroiditis + Alopecia Areata	1
Time from diagnosis	
<5 years	1
>5 years	11
Missing	3

The interview encourages the woman's description of her experience regarding her gestation and the process of becoming mother, investigating the mental representations of this woman as a mother and of her expected baby.

Prenatal Attachment Inventory (PAI; Muller, 1993; Della Vedova et al., 2008; Busonera et al., 2017)

This is designed to measure prenatal attachment according to Muller's (1993) definition. It is composed of 21 items assessed by a Likert scale (ranging from 1 - *almost never* - to 4 - *almost always*). High scores indicate a high grade of prenatal attachment. The reported internal reliability values of Alpha vary from $\alpha = 0.81$ to $\alpha = 0.93$.

Maternal Antenatal Attachment Scale (MAAS; Condon, 1993; Busonera et al., 2016)

This measure assesses *Quality of attachment* (constituted by 11 items) and *Intensity of preoccupation* (defined by 8 items). The high global score denotes a high level of attachment to the unborn baby. The values of Cronbach's α were reported ranging between 0.69 and 0.87.

Dyadic Adjustment Scale (DAS; Spanier, 1976; Gentili et al., 2002)

This instrument (characterized by 32 items) consisted of four dimensions: Affective expression (4 items); Cohesion (5 items); Consensus (13 items); Satisfaction (10 items). Reported internal consistency ranges from 0.73 to 0.96.

Parental Bonding Instrument (PBI; Parker et al., 1979; Scinto et al., 1999)

It assesses the view that adult have of the parenting style of their mothers and fathers. It is composed of 25 items for the mother and 25 items for the father, assessed by Likert scale (ranging from 0 = *very unlike* to 3 = *very like*). The parenting style is evaluated in terms of *care* (12 items) and *control* (13 items). Both the original and italian versions of the instrument showed good internal consistency (from 0.83 to 0.91).

Multidimensional Scale of Perceived Social Support (MSPSS; Zimet et al., 1988; Prezza and Principato, 2002)

This measure (characterized by 12 items) assesses the appropriateness of support from some figures: family, friends, and a significant other. All responses are rated on a 7-point Likert scale and high scores are related with the perception of high levels of social support. This instrument showed good indices of reliability (Alphas from 0.81 to 0.98).

Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977; Fava, 1983)

This test comprises 20 items with responses assessed by a 4-point Likert-type scale. The total scores vary from 0 to 60 (when high scores designate a strong depressive symptomatology). The CES-D values of reliability Alpha coefficients varied from 0.85 to 0.95.

Difficulties Emotional Regulation Scale (DERS; Gratz and Roemer, 2004; Giromini et al., 2012)

It assesses clinically significant difficulties in the process of emotion regulation. The 36 items referred to six dimensions: Difficulties Engaging in Goal-Directed Behavior (5 items); Impulse Control Difficulties (6 items); Lack of Emotional Clarity (5 items); Lack of Emotional Awareness (6 items); Limited Access to Emotion Regulation Strategies (8 items); No acceptance of Emotional Responses (6 items). Questions are assessed by a Likert scale (ranging from 1 - *almost never* - to 5 - *almost always*). The authors reported a good internal consistency ($\alpha = 0.93$).

Health Care Relationship-Trust Scale Revised (HCR-TS; Bova et al., 2012)

This 13-item scale assesses patients' levels of trust in their healthiness care provider. Items are evaluated from 0 to 4. Total scores have a possible range of 0–52 (when higher scores indicate greater levels of trust). Cronbach's alpha was 0.96. This instrument did not have a validation study for the Italian version; therefore, the results were prudently evaluated referring to the original normative sample.

Data Analysis

In order to deepen the complexity of the matter, we applied a mixed methods approach. Specifically, we chose to combine qualitative and quantitative data, emphasizing the convergence of suggestions deriving from different methods that measure related unobserved construct. The subsequent "triangulation" among dissimilar methods and data allows for a full investigation of relevant experimental dimensions (Creswell and Creswell, 2017).

In relation to the application of a qualitative approach, in these preliminary analyzes, we did not use the IRMAG-R coding system provided by the authors, but the transcripts were analyzed applying a methodological approach broadly inspired to the general principles of Grounded Theory. Specifically, in relation to the qualitative analysis of the transcripts, we applied a process of interpretative reconstruction of the information, based on cyclical comparisons of data. These recurrent assessments have supported in this clinical sample a constructive dynamic identification of encoding steps (Cicognani, 2002). This qualitative approach allows us to catch useful clinical insights to understand emotional and/or psychic dynamics activated during pregnancy. In particular, this approach started from the attribution of codes, a progressive reassembly of data, together with a detailed analysis of the same data, to achieve an increasing level of abstraction. We identified 48 *Codes* grouped into six larger *Families* defined as: (1) perception of maternal identity, (2) creation of a mental space for the baby, (3) perception of couple changes, (4) association between pregnancy and autoimmune disease, (5) occurrence of narrative's contradictions, (6) emotions and fears.

Each *Family* was divided into *functional* (N = 27/48 codes) and *dysfunctional* (N = 21/48 codes) *aspects* (**Table 2**). Following the recommendations given by Corbin and Strauss (2008), the data were examined and debated by several researchers. All interviews were recorded, transcribed verbatim, and analyzed using the software Atlas.ti (release 7.5). All interviews were coded by two researchers to ensure multiple perspectives on the data (agreement = 82%).

Regarding the quantitative approach, we analyzed the outcomes of our participants in the validated questionnaires, comparing their scores with the normative samples' means. Specifically, we applied the Student's t to evaluate if the participants' means were different from the normative sample.

RESULTS

In the first phase of work, we evaluated the occurrences of *codes* in the interviews. The most frequent *codes* were (**Figure 1**): *Code* 15 (*Dysfunctional*) *No name for the baby* (N = 357): the mother refers to the baby using neutral terms such as "the baby" and does not use nicknames or the name chosen; *Code* 40 (*Functional*) *Fears* (N = 88): the mother reports fears related or not related to pregnancy which appear to be "natural" in this phase of life (e.g., the fear of delivery); *Code* 42 (*Functional*) *Emotions* (N = 387): the mother talks about her positive and negative emotions.

TABLE 2 | Description of FAMILIES; frequencies and percentage of functional and dysfunctional codes.

Family codes N Functional – Dysfunctional codes (e.g., functional and dysfunctional aspects)	N Functional Frequency (%)	N Dysfunctional Frequency (%)	Total
(1) Perception of maternal identity **5 - 4** (*functional*: code 1. In her narrative, the woman is able to express her own identity as mother; *dysfunctional*: code 2. In her narrative, the woman is unable to express her own identity as mother)	88 (85.5%)	15 (14.5%)	103
(2) Creation of a mental space for the baby **10 - 7** (*functional*: code 10. The woman describes fetus's movements and she describes these movements as traits of the baby; *dysfunctional*: code 15. The woman refers to the baby using neutral terms such as "the baby" and does not use nicknames or the chosen name)	166 (28.2%)	421 (71.8%)	587
(3) Perception of couple changes **8 - 3** (*functional*: code 31. The woman refers to changes in the relationship with the partner such as greater intimacy; *dysfunctional*: code 35. The woman says that nothing has changed in her relationship with her partner during her pregnancy)	48 (73.8%)	17 (26.2%)	65
(4) Association pregnancy-autoimmune disease **1 - 2** *(functional*: code 25. The woman spontaneously reflects on the possible interactions between her own autoimmune disease and pregnancy; *dysfunctional*: code 27. In her narrative, the woman never refers to her own autoimmune disease)	17 (65.3%)	9 (34.7%)	26
(5) Occurrence of narrative contradictions **0 - 4** (*dysfunctional*: code 45. In the interview with respect to the same subject, the woman expresses thoughts in contrast with each other)	/	100 (100%)	100
(6) Emotions and fears **3 - 1** (*functional*: code 42. The woman talks about her positive and negative emotions. *dysfunctional*: code 39. The woman refers irrational fears such as "*I am afraid that with the fetal movements, the membrane will break*")	480 (99%)	4 (1%)	484
N Tot Functional codes: 27/48 **N Tot Dysfunctional codes: 21/48**			

The most frequent *Functional Family Codes* were: (1) Perception of maternal identity (85.5%); (3) Perception

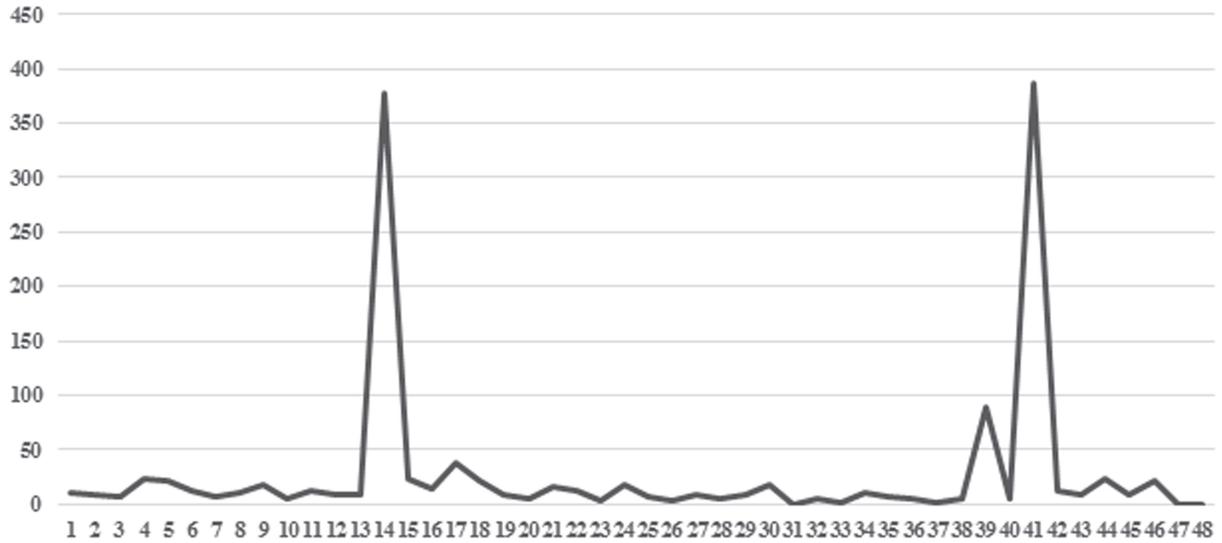

FIGURE 1 | Frequency of 48 codes for 15 interviews. In the axis of the abscissas are the codes; in the axis of the ordinates are the frequencies of the codes.

of couple changes (73.8%); (4) Associations pregnancy-autoimmune disease (65.3%); (6) Emotions and fears (99%).

The most frequent *Dysfunctional Family Codes* were: (2) Creation of a mental space for the baby (71.8%); (5) Occurrence of narrative contradictions (100%) (**Table 2**).

Descriptive statistics of measures and statistical comparison with normative samples are reported in **Table 3**. It is highlighted a significant difference ($df = 14$; $p < 0.01$) between the score of our participants and the mean scores in normative samples in relation to the following scales: DAS Dyadic Cohesion ($t = 5.27$); PBI Paternal Care ($t = -6.58$) and Maternal Care ($t = -8.60$); MSPSS Tot ($t = -5.33$), Family ($t = -3.33$), Friends ($t = -6.77$) and Significant Other ($t = -3.80$); CES-D ($t = 7.40$); DERS Goals ($t = 39.10$); HCR-TS D ($t = -6.44$).

DISCUSSION

The results of our study showed that the participants did not have socio-demographic characteristics that could be considered risk variables (see **Table 1**). Nevertheless, the results from the qualitative and quantitative analyses highlighted some vulnerabilities that could have negative effects on bonding between mother and fetus/child. Qualitative analysis of interviews showed that these women focus in their narratives on greater intimacy with the partner and give less space to the representation of the baby and the construction of the bond with him/her. Furthermore, transcripts are often characterized by statements that are contradicted during the interview and that can refer to each topic addressed. The women did not always spontaneously reflect on the possible interactions between their own autoimmune disease and their pregnancy. Women give much space to the verbalization of emotions, both positive and negative, but the emotions appear more centered on themselves and less on the baby. Moreover, emotions often express contradictory aspects (e.g., a mother with autoimmune thyroid disease says at the beginning of the interview: "I was happy at the news of the pregnancy" and in another part of the interview she claims to have been very ambivalent toward pregnancy although the pregnancy itself was planned; a mother with multiple sclerosis says: "I never thought of the disease as a problem, I never counted a relapse, I didn't want the disease to limit me"; a mother with type 1 diabetes says: "I never imagine the baby; I feels that the baby moves a lot but I don't know what could stimulate these movements; I didn't prepare anything at home for his/her birth" and then she says: "I think I'll be a careful mother"; a mother with multiple sclerosis says "I'm afraid the baby suffers when he moves too much, maybe he moves a lot because he can suffocate. I have feelings of guilt because I drink little so I am afraid that the amniotic fluid will dry up"; a mother with autoimmune thyroid disease says "our sexual activity has increased a lot, we really want to stay close, the feeling has increased. There is more sexual desire but recently it is difficult for this belly that disturbs"). These aspects seem to converge with the results of the quantitative analysis (see **Table 3**).

The women showed a difficulty in regulating emotions (Goals subscale of the DERS "difficulties engaging in goal-directed behavior when emotionally aroused": 38.9 vs. 13.6; CES-D: 32.5 vs. 12.9) and low perceived social support (MSPSS total: 5.16 vs. 6.0). Women also referred memories of low maternal and paternal care (PBI paternal care: 19.4 vs. 25.1; maternal care: 21.1 vs. 27.6) and low trust in the health care provider (HCR-TS: 39.1 vs. 55.3). However, the women reported a high level of attachment to the fetus and a good marital relationship characterized by a high score on the subscale of dyadic cohesion (18.5 vs. 14.6) that indicates the degree of closeness and shared activities experienced by the couple. Despite, the high level

TABLE 3 | Descriptive statistics of measures – statistical comparison with normative sample.

Scale	Mean (sd)	Mean (sd)	Student's *t* (df = 14)
	Participants	Normative sample	
PAI	60.7 (9.1)	60.9 (9.2)	−0.07
MAAS	76.6 (5.3)	78.6 (5.6)	−1.93
DAS			
Tot	115 (30.3)	115.7 (21.6)	−0.13
Dyadic consensus	53.3 (6.0)	51.6 (10.1)	1.05
Dyadic satisfaction	38.2 (8.9)	37.7 (7.7)	0.21
Affectional expression	9.47 (2.5)	9.8 (2.4)	−0.51
Dyadic cohesion	18.5 (2.7)	14.6 (5.2)	5.27**
PBI			
Paternal care	19.4 (3.3)	25.1 (8.1)	−6.58**
Paternal overprotection	13.2 (5.7)	13.5 (8.0)	−0.23
Maternal care	21.1 (2.9)	27.6 (7.5)	−8.60**
Maternal overprotection	14.9 (6.5)	16.3 (8.6)	−0.85
MSPSS			
Tot	5.16 (0.6)	6.0 (0.8)	−5.33**
Family	5.05 (0.9)	5.9 (1.2)	−3.33**
Friends	5.11 (0.5)	6.1 (0.8)	−6.77**
Significant other	5.33 (0.7)	6.0 (1.1)	−3.80**
CES-D	32.5 (9.7)	12.9 (7.8)	7.40**
DERS			
Tot	71.7 (17.9)	73.6 (16.1)	−0.40
Non-accept	12.9 (4.1)	11.2 (3.7)	1.54
Goals	38.9 (2.5)	13.6 (4.4)	39.10**
Impulse	10.3 (3.5)	11.6 (3.4)	−1.46
Awareness	13.5 (4.5)	14.0 (3.7)	−0.45
Strategies	12.9 (4.0)	14.1 (5.0)	−1.12
Clarity	9.2 (3.3)	9.2 (2.6)	0.00
HCR-TS	39.1 (9.7)	55.3 (7.1)	−6.44**

**$p < 0.01$.

of attachment to fetus it seems that in the process of psychic reorganization functional to the construction of the maternal role, these women show a difficulty in holding the baby in their mind almost comparable to the difficulty of their immune system receiving the fetus. This probably leads to the emergence of emotional states that, instead of reorganizing the emotional experience toward the construction of the definition of the parental role and the representation of the other, lead to the emergence of depressive symptoms and low trust in the health care providers and in perceived social support from their network of relationships. The characteristics of the narrative seem to approach the group identified by Ammaniti et al. (2013) as Not Integrated/Ambivalent characterized by confused and contradictory representations, which limit the possibility of a coherent narration of the mother's personal experience while the affective investment is quite high. A subsequent analysis of these interviews through the IRMAG coding system will allow us to verify these data. The literature (Fava Vizziello et al., 1993; Stern, 1995; Rasmussen et al., 2013) highlighted that the difficulty to organize representation of the baby, the occurrence of depression and/or low social support, and memories of low maternal and paternal care can lead to potentially disturbed mother-infant relationships. These preliminary results give interesting insights on the possible impact of autoimmune disease on the redefinition of maternal psychic equilibrium. With the addition of a medical condition, the pregnancy requires constant attention to the woman's emotional and physical well-being. The woman's emotional response can also be affected by changes necessitated by the high-risk condition (e.g., frequent examinations to monitor fetal growth). An ambivalent attitude during pregnancy can predict a higher probability of difficulties in maternal caregiving. Sometimes these complicating emotional and psychosocial factors are overlooked because the attention only focuses on medical conditions. Recognizing mothers' vulnerabilities during pregnancy is important because it underlines the need for a supportive intervention during this period. A good working relationship between the woman and the medical staff is essential so that the woman receives all information about her autoimmune disease and her baby's health in the most appropriate manner. The maternal-fetal immunological interrelationship is an important association between two different individuals. Psychoneuroimmunology has brought forth remarkable insights that highlight how the relational world can "get under the skin" to influence immune, neural, and neuroendocrine processes in ways that might have consequences for later health (Ehrlich, 2019). It's important to reflect on the complexity of the mind-body relationship and on the role of physical and psychic defense mechanisms in the processes of change. The relationship between pregnancy and autoimmune disease refers to the relationship between the role of care and the role of protection. Often pregnancy, with its physiological transformations, acts on the woman's immune system, protecting the woman from the symptoms of the disease. What, then, is the baby's role in the mother's mind? The presence of a medical condition, which can compromise the physical health of mother and baby, often obligates both the mother and the care setting to pay attention to the body of the woman and the fetus/child, neglecting psychological needs, thus supporting a possible mind-body scission. Understanding these aspects is relevant both for supporting mothers and for professionals who follow these women in the perinatal period.

Limitations of the present study are that it included a limited sample size and the heterogeneity of autoimmune diseases with possible different effects on pregnancy. This is due to the difficulty of recruiting the sample in this population. Furthermore, these features of the sample size do not allow to apply more sophisticated statistical analyses. An additional limit of this work might be related to the absence of the control group in this phase of the work. A control group will be used in the next steps of our research, which is actually in progress.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Department of Pedagogy, Psychology, Philosophy at the University of Cagliari (Italy). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SC, JL, and MA contributed equally to the theoretical and empirical aspects of the study, and wrote the final version of the manuscript. FC contributed to the collection and analysis of data. GM contributed in critically revising the manuscript for important intellectual content.

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Hepatitis C Pretreatment Profile and Gender Differences: Cognition and Disease Severity Effects

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Background: The hepatitis C virus (HCV) is known to infect the brain, however, the findings based on associated neuropsychiatric syndrome are controversial and the association itself remains unclear. Gender research in HCV infection is limited, failing to integrate the role of gender differences in neurocognitive syndrome. The aim of this study was to characterize psychological and neurocognitive profiles in HCV-infected patients before treatment and to explore gender differences in those profiles, as well as the impact of disease severity.

Methods: A total of 86 patients diagnosed with chronic hepatitis C were included. Depression and anxiety were assessed using Hamilton anxiety scale (HAM-A), Hamilton depression scale (HAM-D), Beck Depression Inventory (BDI). For cognition, a neuropsychological battery to measure attention, concentration and memory was used, and executive function components validated for the Portuguese population was also used before starting treatment. To identify the disease severity, platelet ratio index, and FibroScan® were used.

Results: A statistically significant gender effect was found on HAM-A (B = 0.64, CI: 0.17–1.11) and HAM-D (B = 0.62, CI: 0.14–1.09), with women scoring higher compared to men. Regarding neuropsychological scores, significant differences between gender were identified in executive functions measured by Trail Making Test (TMT B) (B = 0.48, CI: 0.02–0.97), TMT B-A (B = 0.26, CI: −39.2 to −3.7) and in digit span total (B = −0.52, CI: −1.0 to −0.04), with women performing worse than men. Controlling for years of substance dependence, TMT-B and TMT B-A showed significant gender differences. Regarding the presence or absence of substance dependence, only HAM-A and HAM-D remained significant. For categorical variables, Digit Span Total was also influenced by gender, with women being more likely to be impaired: odds ratio (OR) = 7.07, CI: 2.04–24.45), and a trend was observed for Digit Span Backward (OR = 3.57,

CI: 1.31–9.75). No significant differences were found between disease severity and neurocognitive performance.

Conclusion: Data suggest that gender has an influence on depression, anxiety and cognitive functions with women showing greater impairment compared with men. This effect seems to be influenced by substance dependence.

Keywords: hepatitis C, neurocognition, anxiety, depression, gender, disease severity

INTRODUCTION

Hepatitis C virus (HCV) is one of the most important infections worldwide, with 71 million people infected (Polaris Observatory et al., 2017). Despite the advent of HCV therapies and high rates of cure, if not treated, HCV acute infection tends to progress to chronic state, hepatic cirrhosis (10 to 40%) and hepatocellular carcinoma, which tend to be clinical indications for liver transplant (1 to 5% per year) (Monaco et al., 2015).

Hepatitis C virus patients frequently present neuropsychiatric symptoms, including fatigue, anxiety, depression, and neurocognitive impairment, that have been associated with negative treatment outcomes (Monaco et al., 2015; Dirks et al., 2017; Yarlott et al., 2017). Several studies reported that HCV associated neuropsychological impairments are independent of liver disease stage (excluding cirrhosis) (Monaco et al., 2015; Yarlott et al., 2017), suggesting that, in chronic patients, HCV infection itself might directly cause cerebral dysfunction, contributing to cognitive deficits in patients (Grover et al., 2012). Therefore, the neurocognitive profile of these patients before treatment needs to be addressed, due to the possible implications on the treatment course (e.g., non-adherence-like behavior due to cognitive dysfunction). Additionally, it is important to address other risk factors that can have a negative impact on cognition. Despite the eventual effects of antiviral medication on cognition, the high rate of substance abuse and the prevalence of psychiatric disorders among HCV-infected patients are important factors associated with cognitive impairment that compromises adherence and treatment efficacy (Więdłocha et al., 2017).

Most of the patients with HCV consistently report a significant reduction in health-related quality of life, in comparison with healthy controls (Adinolfi et al., 2017). The psychiatric symptomatology in chronic hepatitis C, in particular depression, is twice as high as in the general population, and it is probably one of the major factors for decreasing quality of life, treatment discontinuation and/or negative treatment outcomes (Monaco et al., 2015).

According to several studies, it has been hypothesized that depression and cognitive impairment might be associated with HCV neurotoxicity (Adinolfi et al., 2015). Recent studies with interferon-free treatment showed that HCV patients presented neuropsychiatric symptoms like fatigue, insomnia, anxiety, depression, and cognitive dysfunction (Gritsenko and Hughes, 2015; Smith et al., 2015; Chasser et al., 2017), supporting the HCV neurotoxicity hypothesis.

In untreated HCV patients, emotional distress and depressive disorders suggest the role of HCV itself in the onset of these neuropsychiatric manifestations (Alavi et al., 2012). In a recent review, the "hepatitis C brain syndrome" was identified as being composed of cognitive impairment, fatigue, and depression. This syndrome is probably generated by peripheral immune responses, affecting the central nervous system (CNS) by a neuroinflammatory response associated with CNS HCV infection and also by negative life events and other psychogenic stressors (Yarlott et al., 2017).

Neurocognitive impairment, one of the most common extrahepatic manifestations of HCV, can lead to subtle changes in processing speed, memory, and cognitive performance (attention, concentration, psychomotor speed, and verbal fluency), and up to 50% of HCV-infected patients can develop clinical or subclinical manifestations of this dysfunction (Lowry et al., 2010; Ferri et al., 2016). Cognitive impairments were previously thought to be associated with the development of hepatic encephalopathy (Gaeta et al., 2013). However, their presence was demonstrated in the absence of advanced liver disease, as well as in the absence of human immunodeficiency virus (HIV) coinfection, depression or substance dependence (Weissenborn et al., 2004; Kuhn et al., 2017; Yarlott et al., 2017). HCV is known to infect the brain; however, findings from studies on associated neurocognitive changes are controversial and it remains unclear whether HCV eradication improves neurocognitive performance (Kuhn et al., 2017).

Regarding gender differences, women with HCV seem to experience stigma, concerns about confidentiality, treatment side effects and lack of engagement with health services, more so than men (Harris and Rhodes, 2013). However, the gender differences research in symptoms profile, as well as in treatment response and treatment adherence, is scarce, albeit crucial to improving medical and psychological integrated interventions.

This study aimed to characterize psychological and neurocognitive profiles in HCV-infected patients before treatment, and to describe gender differences as well as the impact of disease severity in those profiles.

MATERIALS AND METHODS

This research is part of a larger longitudinal protocol including two assessment times, before and after HCV antiviral medication. It was submitted to and approved by the Centro Hospitalar Universitário Lisboa Norte Ethics Committee (Ref. 0536) and the Portuguese Data Protection Authority (No. 6331/2012).

If eligible, subjects were informed about the nature of the study and their voluntary cooperation. After confidentiality assurance, written informed consent was obtained.

Recruitment of Participants

A total of 86 patients diagnosed with chronic hepatitis C were selected from an outpatient clinic through a convenience procedure (Viral Hepatitis Clinic at the Hospital de Santa Maria, Lisbon).

The inclusion criteria were: minimum formal schooling completed with success (at least 4 years education or fluency in reading and writing); ages between 18 and 65 years-old; diagnosis of chronic hepatitis C with detectable HCV RNA viral load for at least 6 months. The exclusion criteria were: presence of neurological or psychiatric disorders that may induce cognitive deficits; major depression according to DSM-V; consumption of opiates, cocaine and/or other recreational drugs in the 6 months prior to the beginning of the assessment; use of medication that may interfere with the study objectives; history of neurological, infectious or tumoural pathology or systemic illness with an impact at CNS level; a Mini-Mental State Examination (MMSE) score below the cut-off for dementia in the Portuguese population; hepatic cirrhosis or severe physical deterioration incompatible with the psychologic and neuropsychologic assessments.

Assessment and Evaluation

A semi-structured interview was performed to collect sociodemographic and clinical data.

Psychiatric Evaluation

Depression

Depressive symptoms were assessed using a patient-rated questionnaire and a clinician administrated one, to control for the bias of self-reporting.

Hamilton Depression Scale (HAM-D)

Depression was assessed using the 17-item HAM-D (Hamilton, 1960). The Hamilton scale was developed for patients diagnosed with depression, to measure its intensity and to identify depressive symptoms profiles. We used the cut-off scores validated for the Portuguese population (Vaz Serra, 1972).

Beck Depression Inventory (BDI)

Beck published the "Inventory for Measuring Depression" in 1961, representing the first self-assessment questionnaire for the study of depression (Beck et al., 1961). The inventory comprises 21 symptoms that cover multiple aspects of depressive manifestations, not only affective but also cognitive, motivational and behavioral. In this study, the translated and validated Portuguese version was used (Vaz Serra, 1972).

Anxiety

Hamilton Anxiety Scale (HAM-A)

Anxiety was assessed using the 14-item HAM-A (Hamilton, 1959). The Hamilton scale for anxiety comprises 14 symptoms covering the most characteristic manifestations of the anxious syndrome, both in terms of "psychic" (items 1 to 6) and "somatic" (items 6 to 14) symptoms. This scale is an instrument that has long been validated by several studies and measured for different Portuguese populations (Vaz Serra, 1972).

Neuropsychological Evaluation

Mini-Mental State Examination (MMSE)

The MMSE is one of the most widely used brief instruments for the clinical evaluation of global cognitive state in adults (Folstein et al., 1975). The MMSE is used for the evaluation of the mental state and screening of dementia. It is a 30-point questionnaire, measuring the following areas of cognitive function: time orientation, spatial orientation, registration, attention and calculation, recall, language, repetition, and visual construction. The normative cut-off values for the Portuguese population adjusted to education were used (Guerreiro et al., 1994).

Trails Making Test (TMT)

The TMT is an instrument that measures executive functions (Reitan, 1958). It consists of two parts. In Part A, the subject is instructed to connect a set of 25 numbers as fast as possible, while still maintaining accuracy. In Part B, the subject is instructed to connect numbers sequentially with letters. Scoring is expressed in terms of the time (in seconds). The TMT B-A score (calculated as the difference between TMT-B and TMT-A, to remove the individual motor speed element from the task and the composite) is considered a measure of cognitive flexibility relatively independent of manual dexterity (Misdraji and Gass, 2010). The Portuguese-validated version was used (Cavaco et al., 2013).

The Battery of Lisbon for the Assessment of Dementia (BLAD)

The BLAD is a comprehensive neuropsychological battery evaluating multiple cognitive domains and validated for the Portuguese population (Guerreiro, 1998). Tests of interest for the present study were Digit Span (DS) and Logical Memory (immediate and delayed recall). DS is a test that evaluates immediate memory (Digit Span Forward), working memory (Digit Span Backward), and attention and concentration (Digit Span Total). Logical Memory (immediate or delayed recall) evaluates verbal memory and learning. The participants below education and age-adjusted values for the Portuguese population (1 standard deviation) were considered impaired. A cut-off value of 1 standard deviation was adopted, considering that the use of the cut-off value of 1.5 standard deviations (Petersen et al., 1999) could exclude subjects that, from a clinical point of view,

suffered from mild cognitive impairment (Winblad et al., 2004; Coelho et al., 2017).

Disease Severity

Aspartate Aminotransferase (AST) to Platelet Ratio Index (APRI)

This APRI is among the best-validated methods for predicting HCV progression (Wai et al., 2003). The lower the APRI score (<0.5), the greater is its negative predictive value (and ability to rule out cirrhosis); the higher the value (>1.5), the greater the positive predictive value (and ability to rule in cirrhosis). The APRI helps with diagnosis based on the platelet count and AST level. The APRI alone is likely not sufficiently sensitive to rule out the significant disease. Some evidence suggests that the use of multiple indices in combination, such as APRI plus findings on transient hepatic elastography, or an algorithmic approach, may result in higher diagnostic accuracy than using APRI alone (Chou and Wasson, 2013).

Transient Hepatic Elastography (TE)

Liver stiffness measurement by TE was performed according to published recommendations, using the M probe of FibroScan®. The results were expressed in kPa. Only procedures with at least 10 validated measurements, >60% success rate and an interquartile range inferior to 25% of the median value were considered reliable (Pons et al., 2017). The standard 12.5 kPa for the diagnosis of cirrhosis was used (Manuel Echevarría et al., 2015).

Statistical Analysis

Results were analyzed using descriptive statistics, including percentages to describe categorical variables and means and standard deviations for continuous ones. Spearman correlation were used to analyze the eventual relation between HCV infection duration and cognitive/psychological evaluation results.

Demographic, clinical, psychological and neuropsychological data were analyzed using independent *t*-tests or linear regression models for dependent continuous variables, as normality was achieved in every distribution. Data were tested for normality using the Shapiro–Wilk test (Ghasemi and Zahediasl, 2012). The continuous variables were all standardized to the mean and standard deviation (*Z* score), and the reported B values represent the standardized coefficients or the dimension of the effect. Every B value between 0.2 and 0.5 was considered to be presenting a relevant effect, and above 0.5 were considered to be of medium dimension. Although the significance (*P*-value) is presented and the significance value was established at a two-tailed threshold of <0.05, all interpretation is based on the concomitant values of the coefficient B and the *P*-value, following recent discussion on the interpretation bias caused by the sole interpretation of the latter (Sullivan and Feinn, 2012; Lakens et al., 2018).

For categorical analysis, chi–squared tests (with the report of Cochran's and Mantel-Haenszel statistics (odds ratio) were used when just one independent variable was being tested or logistic regression models, when there was more than one independent variable. The values reported for this analysis are the ORs, with a reference neutral value of 1. Once again, a balanced analysis between the odds ratio and the respective *P*-value was reported. Odds ratio superior to 1.5 or inferior to 0.75 were considered as relevant. All the neuropsychological tests were categorized with the value of 1 for defect and 0 for the absence of defect, and women were categorized as 1 and men as 0.

The variables related to disease severity (APRI and FibroScan® values) are both continuous. Patients with a level of APRI and FibroScan® value superior to 2.5 standard deviations of the respective mean were excluded from the sample, as their level of disease severity was found to be compromising the normality of the analysis (Leys et al., 2013). Three males fell under this condition.

Results are presented controlling for years of substance dependence (A.Beta1) and the presence or absence of previous illicit drugs consumption (A.Beta2), as a statistically significant difference between males and females was found. Beta (B) scores represent the influence of the gender over the psychological or neuropsychological measures and the respective standard deviations for a significance at 95%. Beta values higher than 0.20 represent an effect at the sample level.

The reported values are ORs, adjusted ORs for the number of years of substance dependence (A.ORs) and the presence or absence of illicit drugs consumption (A.OR1); a confidence interval of 95% was established.

Statistical analyses were performed using IBM SPSS Statistics 23 for Windows (2016; IBM Corp, Armonk, NY, United States). The statistical methods of this study were reviewed by Isabel Flores, senior consultant in biostatistics.

RESULTS

Demographic and Clinic Characterization Data

The sample consisted of 86 HCV-infected patients, 63 men, mean age 47.7 ± 9.9 and 23 women (48.0 ± 8.8), submitted to psychological and neuropsychological assessments. There were no statistically significant differences between genders related to age, diagnosis time, civil status, education, employment, psychiatric antecedents, years of substance dependence, psychoactive substances, alcohol use or smoking. There were statistical differences in substance dependence (89.5% for men and 50% for women, $P < 0.001$) (**Table 1**).

Differences in Psychological and Neuropsychological Tests by Gender

There were two levels of analyses: the effect of gender on the continuous variables, and the effect of gender on each neuropsychological indicator classified in two categories - with

TABLE 1 | Demographic and personal characterization with gender comparison.

	Females, *n* = 23	Males, *n* = 63	*P*
Age	48.0 ± 8.8	47.7 ± 9.9	0.87
Time diagnosis, in yr	9.9 ± 8.6	7.5 ± 7.3	0.24
Education, in yr	9.9 ± 3.3	9.6 ± 4	0.78
Civil status			0.9
Single	18.2%	18.3%	
Married	50%	53.3%	
Divorced/separated	27.3%	26.7%	
Widowed	4.5%	1.7%	
Employment			0.83
Employed	54.5%	53.3%	
Unemployed	31.8%	38.3%	
Medical leave	4.5%	1.7%	
Retired	9.1%	6.7%	
Psychiatric antecedents	27.3%	11.7%	0.08
Substance dependence	50%	89.5%	0.001[a]
Psychoactive substances			0.40
Heroin	36.4%	43.4%	
Cocaine	9.1%	22.6%	
Heroin + Cocaine	18.2%	5.7%	
Marijuana	36.4%	28.3%	
Years of substance dependence	17.0 ± 9.1	17.2 ± 10.7	0.97
Alcohol			0.41
No	86.4%	78.3%	
<10 g/day	13.6%	20%	
≥10 g/day	4.5%	3.3%	
Smoking			0.55
No	45.5%	33.3%	
<10 cigarettes/day	31.8%	43.3%	
≥10 cigarettes/day	22.7%	23.3%	

[a]*P < 0.01.*

or without cognitive defect (**Tables 2**, **3**). A linear regression model was used to evaluate the gender effect on psychological and neuropsychological performance.

Regarding gender, it was possible to identify significant effects on HAM-A (B = 0.64, confidence interval (95% C.I.): 0.17–1.11), with women having higher scores on anxiety. The same type of effect was found on HAM-D, with women obtaining a higher significance (B = 0.62, 95% C.I.: 0.14–1.09) in depression. No difference between genders was found on the BDI.

In neuropsychological tests, we found significant differences between gender in executive functions measured by TMT-B (B = 0.48, 95% C.I.: 0.02–0.97) and in TMT B-A (B = 0.26, 95% C.I.: −39.2 to −3.7), with women performing worse.

Digit Span Total was also influenced by gender (B = −0.52, 95% C.I.: −1.0 to −0.04), with women having a lower score. Controlling for years of substance dependence, Digit Span Total was no longer significant; however, TMT-B and TMT B-A continued showing gender differences. Controlling for the presence or absence of substance abuse, only HAM-A and HAM-D remained significant.

The duration of the infection did not influence psychological or cognitive results. In fact, we performed a correlation analysis (spearman) between time since the diagnosis and neurocognitive/psychological variables and we only found a weak correlation with TMT B-A (r = −0.252 p = 0.027).

To evaluate the association between gender and neuropsychological results, categorized as with or without defect analysis, logistic regression models were used.

In terms of the odds ratio, Digit Span Total shows a very relevant result, with women having a 7-times higher possibility of scoring at an abnormal level in this indicator than men (ORs = 7.07, 95% C.I.: 2.04–24.45). After adjustment, the ORs remained significant and with a relevant dimension (A.ORs = 6.86, 95% C.I.: 1.88–24.96; A.OR1 = 5.77, 95% C.I.: 1.53–21.88). For Digit Span Backward, a gender effect was significant only in ORs (ORs = 3.57, 95% C.I.: 1.31–9.75), but was lost after adjustments.

Another relevant difference was found in Logical Memory (immediate recall) OR adjusted for years of substance dependence, where women showed a higher percentage of

TABLE 2 | Gender effect in psychological and neuropsychological evaluations.

	Females, *n* = 23	Males, *n* = 63	Beta (95% C.I.)	A.Beta1 (95% C.I.)	A.Beta2 (95% C.I.)
HAM-A	14.3 ± 5.2	10.5 ± 6.0	0.64[b] (0.17 to 1.11)	0.81[b] (0.35 to 1.29)	0.72[b] (0.22 to 1.24)
HAM-D	10.2 ± 4.2	7.3 ± 4.6	0.62[a] (0.14 to 1.09)	0.74[b] (0.26 to 1.24)	0.65[a] (0.13 to 1.16)
BDI	8.7 ± 8.1	7.8 ± 8.4	0.11 (−0.38 to 0.60)	0.12 (−0.39 to 0.63)	0.23 (−3.0 to 0.77)
TMT-A	50.3 ± 6.6	44.6 ± 13.6	0.39 (−0.36 to 0.15)	0.36 (−0.16 to 0.88)	0.24 (−0.28 to 0.77)
TMT-B	134.6 ± 49.8	111.1 ± 49.8	0.48[a] (0.02 to 0.97)	0.53[a] (0.02 to 1.05)	0.31 (−0.20 to 0.83)
TMT B-A	84.3 ± 35.2	62.8 ± 35.9	0.26[a] (−39.2 to −3.7)	0.2[a] (−39.9 to −2.6)	0.17 (−33.2 to 4.28)
Digit span forward	5.3 ± 1.4	5.9 ± 1.2	−0.44 (−0.92 to 0.04)	−0.45 (−0.96 to 0.05)	−0.21 (−0.72 to 0.30)
Digit span backward	3.2 ± 0.9	3.7 ± 1.1	−0.44 (−0.92 to 0.04)	−0.28 (−0.78 to 0.21)	−0.25 (−0.77 to 0.27)
Digit span total	8.6 ± 2.0	9.7 ± 2.1	−0.52[a] (−1.0 to −0.04)	−0.44 (−0.94 to 0.06)	−0.27 (−0.77 to 0.23)
Logical memory (immediate recall)	7.5 ± 2.6	6.8 ± 2.6	0.24 (−0.25 to 0.73)	0.33 (−0.18 to 0.85)	0.31 (−0.22 to 0.84)
Logical memory (delayed recall)	6.6 ± 2.1	5.9 ± 2.4	0.03 (−0.52 to 0.46)	0.05 (−0.20 to 0.25)	−0.08 (−0.63 to 0.45)

Data is presented as mean ± standard deviation, unless otherwise indicated. [a]*P < 0.005;* [b]*P < 0.001. BDI, beck depression inventory; C.I., confidence interval; HAM-A, hamilton anxiety scale; HAM-D, hamilton depression scale; TMT, trails making test.*

TABLE 3 | Association between gender and neuropsychological results, categorized as with or without defect.

		Males (0), *n* = 63	Females (1), *n* = 23	ORs (95% C.I.)	A.ORs (95% C.I.)	A.OR1 (95% C.I.)
TMT-A	No defect (0)	83.3%	83%	1.05	0.96	1.07
	Defect (1)	16.7%	17%	(0.94–3.76)	(0.25–3.63)	(0.26–4.27)
TMT-B	No defect (0)	73.3%	52.2%	2.5	2.48	1.98
	Defect (1)	26.7%	47.8%	(0.92–6.84)	(0.87–7.07)	(0.67–5.88)
Digit span forward	No defect (0)	88.3%	73.9%	2.7	2.35	2.05
	Defect (1)	11.7%	26.1%	(0.78–9.04)	(0.65–8.44)	(0.54–7.86)
Digit span backward	No defect (0)	73.3%	43.5%	3.57[a]	2.49	2.82
	Defect (1)	26.7%	56.5%	(1.31–9.75)	(0.85–7.27)	(9.62–8.31)
Digit span total	No defect (0)	91.7%	60.9%	7.07[b]	6.86[b]	5.77[b]
	Defect (1)	9.3%	29.1%	(2.04–24.45)	(1.88–24.96)	(1.53–21.88)
Logical memory (immediate recall)	No defect (0)	26.7%	47.8%	0.39	0.28[a]	0.39
	Defect (1)	73.3%	51.2%	(0.14–1.07)	(0.09–0.83)	(0.13–1.16)
Logical memory (delayed recall)	No defect (0)	35%	39%	0.84	0.720	0.66
	Defect (1)	65%	61%	(0.31–2.25)	(0.95–1.02)	(0.22–1.20)

[a]P < 0.005; [b]P < 0.001. OR, odds ratio; TMT, trails making test.

normal results, presenting a lower possibility of verbal memory and learning defect (A.ORs = 0.28, 95% C.I.: 0.09–0.83). All the other indicators showed no relevant differences between genders.

Although not reaching a significant level, ORs in TMT-B and Digit Span Forward showed a trend to a worse performance in women, with a probability up to 2.5-times higher for a defect, facing men.

Disease Severity, Gender, Psychological, and Neuropsychological Measures

The possibility of a defect was assessed using as predictors gender, APRI, and FibroScan® values, as measures of disease severity. For psychological dimensions, results were obtained following a multivariable linear regression model and the values reported are the standardized coefficients of the variables (Beta); the Nagelkerke (R^2) represents a measure of goodness of fit. For neuropsychological ones, the indicators were codified as "with defect" (1) and "without defect" (0), and a multiple logistic binary regression was performed (**Table 4**). The mean APRI score for our study population was 0.77 ± 0.68 and for fibroscan was 8.35 ± 4.32. In APRI, as a predictor of disease progression, individuals were below the value representative of cirrhosis (<1.5), as well as in fibroscan evaluation (<12.5 Kpa).

Results showed that disease severity has no relevant effect on any score and only gender had a small predictive capacity for HAM-A (B = 0.62, 95% C.I.: 0.12–1.09; R^2 = 0.13) and for HAM-D (B = 0.56, 95% C.I.: 0.09–1.06; R^2 = 0.12), confirming what had already been reported from the previous analysis.

Digit Span Total provided the most relevant result (Nagelkerke R^2 = 0.23) fully explained by gender, and once again disease severity seemed not to have influence on this score. The OR of 8.01 showed that women have a possibility of about 8 times higher for being classified as with defect on this indicator (B = 8.01, 95% C.I.: 2.01–31.97; R^2 = 0.23). In the presence of disease severity, the Digit Span Backward had a 3.6 higher chance of being classified as a defect (B = 3.60, 95% C.I.: 1.24–10.49; R^2 = 0.10), in the same line of what has been described before.

TABLE 4 | Association between gender, psychological and categorized neuropsychological results, controlling for disease severity.

Psychological	Gender Beta (95%C.I.)	APRI Beta (95%C.I.)	FibroScan® Beta (95%C.I.)	R^2
HAM-A	0.62[a] (0.12–1.09)	−0.33 (−6.79–0.13)	0.05 (−0.17–3.44)	0.13
HAM-D	0.56[a] (0.09–1.06)	−0.23 (−0.64–0.51)	0.07 (−0.23–2.8)	0.12
BDI	0.21 (−0.26–6.94)	−0.25 (−0.59–0.09)	0.01 (−0.27–2.35)	0.04
Neuropsychological	**Gender OR**	**APRI OR**	**FibroScan® OR**	**Nagelkerke (R^2)**
TMT-A	0.83 (0.19–3.59)	0.39 (0.09–1.56)	1.20 (0.56–2.58)	0.05
TMT-B	3.04 (0.99–9.38)	0.68 (0.27–1.72)	0.51 (0.24–1.72)	0.15
Digit span forward	3.62 (0.95–13.75)	0.86 (0.27–2.72)	1.46 (0.58–2.51)	0.96
Digit span backward	3.60[a] (1.24–10.49)	1.0 (0.44–2.23)	1.1 (0.57–1.84)	0.10
Digit span total	8.01[b] (2.01–31.97)	0.81 (2.36–2.78)	0.95 (0.24–1.52)	0.23
Logical memory (immediate recall)	0.39 (0.13–1.13)	0.82 (0.37–1.80)	1.04 (0.58–1.87)	0.05
Logical memory (delayed recall)	0.91 (0.31–2.63)	1.48 (0.65–3.37)	0.90 (0.51–1.59)	0.02

[a]P < 0.005; [b]P < 0.001. C.I., confidence interval.

DISCUSSION

Gender research in HCV infection is limited, failing to integrate the role of gender in neurocognitive syndrome. To the best of our knowledge, our study is the first to explore the gender effect in pretreatment HCV-infected patients.

According to our results using clinician-rated instruments (HAM-A and HAM-D), women presented mild levels of anxiety

and depression and men showed only mild levels of anxiety. In the self-evaluation questionnaire (BDI), men and women scored below the cut-off level for the diagnosis of clinical depression, ultimately due to a devaluation in emotional self-report.

On neuropsychological performance in pretreatment HCV-infected patients, the gender effect was even more evident. Domains, such as attention, concentration, and memory (short-term and working memory), the ability to shift strategy, executive functions and visual-spatial working memory, showed significant differences with women being more impaired than men. Additionally, when participants were categorized as with or without defect, women performed poorly in short-term and in working memory and attention. This gender effect for executive functions was lost when controlling for substance dependence but was maintained and stood out as being significant for attention, concentration and working memory.

These results can be explained due to the gender impact of the disease. Previous findings suggest a significantly higher impact on the quality of life and also a higher burden of the hepatitis C diagnosis in women (Modabbernia et al., 2013). In fact, in the general population, the prevalence of depressive disorders is higher in women (World Health Organization [WHO], 2016), with a greater burden of mood and anxiety disorders and a lifetime prevalence around 21% compared to 13% in men (Kessler et al., 1993).

The impact of psychosocial factors associated with these disorders are also higher in women, and the risk of developing mood disorders associated to adverse life events imply several contributing factors, such as family, work, environmental-related stressors, poor social support or childhood abuse (Alexander, 2007). Biological sex-related variables are also a major determinant of risk for depression, as well as coping with a chronic disease, such as hepatitis C (Kessler et al., 1993). These factors might, perhaps, enhance vulnerability to the neurotoxic effects of the virus in addition to the burden of the disease (Dannehl et al., 2014). In subsequent analysis, our data replicated previous findings of gender effect, with women presenting higher scores in depression and anxiety, even when controlling for drug use and years of substance dependence. Years of drugs misuse seems to be important for verbal memory and learning, with men scoring worse than women. Although these results highlighted the impact of several years of drug use, they do not fully explain the impairment in cognitive functions in our sample. Therefore, these results are in agreement with several literature reports that have highlighted the CNS toxicity of HCV (Forton et al., 2001).

Disease severity does not seem to influence gender effect, or the profile displayed by patients, perhaps due to its low variability in our sample – Fibroscan (men 8.42 ± 4.22; women 8.42 ± 3.98); APRI (men 0.79 ± 0.69; women 0.55 ± 0.31).

The psychological and neurocognitive characterizations of these patients before treatment assumes particular significance. The importance of preventing and treating psychological comorbidities, such as depression and anxiety, can lead to a better quality of life and better overall functioning during treatment. Impairments due to psychological or neurocognitive symptoms are likely to interfere with the way patients experience and cope with treatment (Barreira et al., 2019). The use of a personalized and patient-centered approach, promoting a deeper understanding of disease state and needs, is also desirable (Schaefer et al., 2012; Modabbernia et al., 2013).

Moreover, factors like gender, depression, psychiatric diagnosis in general, illicit drug use, HIV coinfection, treatment regimen, and hemoglobin levels are variables identified as being significantly and consistently associated with adherence/non-adherence (Lieveld et al., 2013). According to a review, there is a tendency for males with HCV to be more adherent than females (Mathes et al., 2014). Although inconclusive, this tendency is consistent with recent findings in the wider chronic illness population. In addition, women were reported as being less likely to receive long-term medical treatment and to engage in clinically recommended monitoring (Manteuffel et al., 2014). These factors are equally relevant in the new treatment landscape because they are independent of treatment duration.

Furthermore, HCV-related morbidity and mortality impose a great burden on societies and public health services. These insights may allow for the design of targeted interventions being aware of personal variables linked to the HCV patient profile before treatment, helping to maximize intervention efficacy and behavior modification, in order to prevent non-adherence and treatment failure. Additionally, psychological and neurocognitive factors are also important for more complex combinations of HCV enzyme inhibitors, becoming increasingly important for achieving treatment success as resistant mutations may develop (Gritsenko and Hughes, 2015).

Research suggests that depression in HCV-infected patients may be under-diagnosed, thereby increasing the risk of treatment discontinuation and depression severity, being that HCV itself is a risk factor for depression (Fialho et al., 2017).

The research presented herein has several limitations. The convenience sampling method and the relatively small sample sizes, particularly for women, is a major limitation. Time-since-diagnosis in a wide range and the non-existence of a matched control group are also relevant limitations. However, to compensate for this limitation, we used the values adjusted for the Portuguese population (education and age-adjusted) for the tests applied. Also, since the majority of patients were naïve at the time of sample collection, we did not control for previous treatments. These results will require verification in larger samples, and our conclusions must be interpreted with caution and are not generalizable to all HCV-infected patients.

Despite these limitations, this study has important strengths. The "hepatitis C brain syndrome" is a very interesting issue and there is a lack of studies exploring potential gender differences regarding this syndrome, using a representative sample. In contrast to the many studies that have relied solely on self-reported symptoms scales, this study used both when assessing the severity of depressive symptoms. The clinician administrated instruments were applied by a single trained clinical psychologist, preventing bias on assessment. In addition, this study also used culturally adapted and validated measures for assessing

psychological and neuropsychological symptoms, and all patients were followed in a single center. Lastly, the results of this study might also have important implications for clinical practice. These findings are also important to encourage mental health professionals to take an active role in HCV treatment in the post-interferon era (Chasser et al., 2017).

CONCLUSION

In conclusion, chronic HCV infection is known to be associated with neuropsychiatric dysfunction. Recognition of neurocognitive symptoms is important before and during the treatment of these patients, but it is noteworthy that neurocognitive and neuropsychiatric symptoms (depression, anxiety, and cognitive disorders) may be associated with direct HCV neurotoxicity.

According to our investigation, gender seems to have an influence on depression, anxiety and some of the indicators of cognitive functions, in chronic HCV-infected patients before treatment.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Centro Hospitalar Universitário Lisboa Norte ethics committee (Ref. 0536). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

All authors conceived and designed the work, revised the manuscript critically for important intellectual content, and approved the final version of the manuscript to be submitted. DB, RF, and SO conceived of the study and participated in the design and coordination. RM, MB, and SO reviewed this manuscript. IF analyzed the data.

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Two Reasoning Strategies in Patients With Psychological Illnesses

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Hyper-emotion theory states that psychological disorders are conditions in which individuals experience emotions that are appropriate to the situation but inappropriate in their intensity. When these individuals experience such an emotion, they are inevitably compelled to reason about its cause. They therefore develop characteristic strategies of reasoning depending on the particular hyper-emotion they experience. In anxiety disorders (e.g., panic attack, social phobia), the perception of a disorder-related threat leads to hyper-anxiety; here, individuals' reasoning is corroboratory, adducing evidence that confirms the risk (*corroboratory strategy*). In obsessive-compulsive disorders, the threat of having acted in an irresponsible way leads to both hyper-anxiety and guilt; here, individuals' reasoning is refutatory, adducing only evidence disconfirming the risk of being guilty (*refutatory strategy*). We report three empirical studies corroborating these hypotheses. They demonstrate that patients themselves recognize the two strategies and spontaneously use them in therapeutic sessions and in evaluating scenarios in an experiment.

Keywords: hyper-emotion theory, emotions, reasoning, anxiety disorders, obsessive-compulsive disorders, corroboratory strategy, refutatory strategy

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INTRODUCTION

The maintenance of psychological illnesses and their resistance to change have a paradoxical nature: people who worry about a certain catastrophe continue to experience fear despite the evidence of their survival. Cognitive models of psychopathology focus their attention on the dysfunctional beliefs implicated in the genesis and maintenance of these illnesses (e.g., Beck, 1976; Harvey et al., 2004; Johnson-Laird et al., 2006). The hyper-emotion theory of psychopathology is in line with these cognitive models (Johnson-Laird et al., 2006; Mancini et al., 2007). Such a model states that psychological disorders are conditions in which individuals experience emotions that are appropriate to the situation but inappropriate in their intensity. The hyper-emotion model is based on a cognitive view where the emotions are related to conscious or unconscious evaluations. These evaluations predispose individuals to certain thoughts and actions (Oatley and Johnson-Laird, 1987). Hence, when individuals are experiencing a hyper-emotion, they are inevitably compelled to reason about its cause, and, over the long term, their ability to reason in this way increases

(cf. Gangemi et al., 2013). As a consequence, patients acquire specific reasoning strategies that depend on the hyper-emotion elicited by the disorder-related threat. The paradox is that these strategies serve to support the psychological disorders, leading as they do to the continued confirmation of the dysfunctional beliefs central to them. In anxiety disorders, such as hypochondria, panic attack, and social phobia, the perception of a disorder-related threat leads to hyper-anxiety. Prudent cognitive processes are thus oriented toward corroborating the danger in order to avoid it or prevent it, because it is "better to be safe than sorry" (e.g., de Jong et al., 1997, 1998; Smeets et al., 2000). For example, de Jong et al. (1998) showed that hypochondriac individuals were more likely to select confirming information when judging a danger related to a conditional hypothesis about physical health (e.g., *If a person suffers from a headache, then that person must have a brain tumor)*, and disconfirming information of the safety conditional hypothesis. The reasoning of anxiety disorder patients should therefore be corroboratory, adducing only evidence that prudentially confirms the risk. We refer to this as the "corroboratory" strategy.

In certain cases, such threats may be associated with the guilt emotion and responsibility, which have been proven to have a key role in the onset and maintenance of Obsessive-Compulsive Disorder (OCD; e.g., Shapiro and Stewart, 2011; Mancini and Gangemi, 2015). In fact, Shapiro and Stewart (2011) showed that: (1) in non-clinical samples, guilt determines obsessive-compulsive-like symptoms, together with an increased perception of threat (see Gangemi et al., 2007), over-responsibility, and intrusive thoughts/impulses (Niler and Beck, 1989); and, (2) in neuro-imaging studies of non-clinical samples, the state of guilt activates brain regions in proximity to OCD-affected regions (Shin et al., 2000; Takahashi et al., 2004). In obsessive patients, cognitive processes should therefore aim to exclude the possibility of guilt for having done something wrong from leading to, for example, risk of contamination. If one wants to falsify a risk with certainty, s/he can only try to imagine all the situations in which the condition could be true and falsify them one by one. Accordingly, obsessive patients should focus on all the possibilities that could put them at risk and then try to refute them beyond reasonable doubt. This strategy is chosen because it is not possible to act on the facts themselves, for example, by changing them (I cannot go back and avoid touching a contaminating photograph). In this case, not only the results obtained but also one's own efforts are evaluated against very high standards. The ultimate goal of this strategy is to avoid the self-accusation of having not been up to fulfilling one's duties. This goal has a paradoxical effect: it suggests possible mechanisms by which the risk could be real (see Johnson-Laird et al., 2006). The reasoning of obsessive-compulsive patients should therefore be refutatory, searching for evidence to refute the risk. We accordingly refer to this reasoning strategy as "refutatory." Unlike the corroboratory strategies in anxiety disorders, so far, no studies have investigated the refutatory form of reasoning in obsessive patients. Only the obsessive-like step-by-step reasoning from a neutral situation toward an unlikely catastrophic consequence, examined by Giele et al. (2011) is comparable to the hypothesized refutatory pattern of reasoning. The obsessive-like step-by-step reasoning form would induce uncertainty and increase the perceived probability of a negative outcome. But, in their study, the authors did not evaluate whether participants, when engaging in this step-by-step reasoning, try to find counterexamples of the obsessive-like consequence, although it would be plausible that the experiment also induced some form of refutatory reasoning.

Here are two vignettes illustrating the contrasting types of reasoning strategies but using contents suggestive of hypochondria (in Johnson-Laird et al., 2006).

The first vignette illustrates corroboratory reasoning:

I'm afraid of the slight pain I feel in my abdomen on the same side as my liver. It could be a symptom of cancer, a liver cancer. I remember an uncle of mine who died from liver cancer after a lot of suffering. In the beginning, his symptoms were the same as mine: he had a similar stomach ache. He didn't take any notice, and the doctors told him that he wasn't ill. But meanwhile, the cancer was spreading. Now, in the same way, the cancer may be spreading in my abdomen. Moreover, it seems to me that I look unhealthy; my tongue is pasty; sometimes I have a bitter taste in my mouth. I look pale, and I could be anemic.

This second vignette illustrates refutatory reasoning:

I'm afraid of the slight pain I feel in my abdomen on the same side as my liver. It could be a symptom of cancer, a liver cancer. I remember an uncle of mine who died from liver cancer after a lot of suffering. But he was in his eighties, and a liver cancer at my age is not common. On the other hand, it's not impossible. Moreover, it seems to me that I look unhealthy; my tongue is pasty; sometimes I have a bitter taste in my mouth. I look pale, and I could be anemic. Of course, these are common symptoms. But they are there, and they are not incompatible with cancer. Moreover, they don't exclude it.

In an earlier study (Johnson-Laird et al., 2006), we showed that psychiatrists distinguish the two strategies as hyper-emotion theory predicts: corroboratory reasoning as the hallmark of patients suffering from various sorts of anxiety disorders, and refutatory reasoning as the hallmark of obsessive patients. Moreover, they do so even when the contents of vignettes, as in the examples above, provide no clue to the disorder. The aim of the present studies, however, was to test whether patients themselves recognize the two strategies (Experiment 1) and spontaneously use them in therapeutic sessions (Experiment 2). As there are still no studies that have investigated the origin of refutatory reasoning strategies in obsessive patients, in a third study (Experiment 3) we wanted to examine whether this form of reasoning actually stems from the (hyper-) guilt emotion.

EXPERIMENT 1

The aim of this study was to verify whether patients themselves recognize their own reasoning strategy. It therefore used the same six matched pairs of vignettes used in the experiment with psychiatrists, including the pair in the Introduction, with the same contents. Hyper-emotion theory (e.g., Johnson-Laird et al., 2006) predicts that those suffering from anxiety will tend to see the corroboratory style of reasoning as being more similar to their

own, whereas those suffering from obsessive-compulsive disorder will tend to see the refutatory style of reasoning as being more similar to their own.

Method

Participants

The experiment tested two groups of patients: 18 patients with obsessive-compulsive disorder (male: 8; age: M = 32.7, SD = 7.5), and 20 patients with anxiety disorders (general anxiety disorder: 4, panic attack: 4, social phobia: 4, specific phobia: 4; hypochondria: 4; male: 14; age: M = 35.8, SD = 5.9). The two groups were similar in age (Mann–Whitney U = 167, *ns*) and educational level (obsessive patients: M = 14.4 years, SD = 1.7, anxiety patients: M = 14.2 years, SD = 1.7, Mann–Whitney U = 718, *ns*). Both groups were undergoing treatment at the Centre for Cognitive Psychotherapy in Rome but were not taking any medication. They were at the beginning of treatment and had been diagnosed through the Structured Clinical Interview and diagnosis for OCD and anxiety disorders in DSM-IV-TR (SCID; First et al., 1996).

Design, Materials, and Procedure

All participants read the same six matching pairs of vignettes as those employed in the earlier study of psychiatrists (see the two examples above; Johnson-Laird et al., 2006). Each pair illustrated the contrasting types of reasoning strategies (corroboratory vs. refutatory). The vignettes had been created based on the typical content of six psychological illnesses: Obsessive-Compulsive Disorder (of two types, one concerning contamination and the other concerning the checking compulsion), hypochondria, generalized anxiety, specific phobia, and paranoia (For translations of the vignettes from the original Italian language into English, see the **Supplementary Appendix**).

Patients were asked whether they wanted to take part in a study of the way people who ask for psychological help reason about certain crucial topics. They were told that there were no right or wrong answers and that it was their opinions that were of interest to the study. Before reading each vignette, the key question in the instructions they were given was this: *How similar is this vignette to how you reason when you think of what you are worried about because of your disorder?* The participants rated similarity on a seven-point Likert scale (from 0 = not similar at all, to 7 = absolutely similar). After having read each vignette, they were asked to describe the cues, if any, they used in evaluating the similarity. The vignettes were presented to the patients in a different single random order.

Data Analysis

A research assistant, blind to the aim of the study, coded all paper data. Since our data were not normally distributed across groups, as assessed by Shapiro–Wilk's test (all Ps < 0.05), we employed non-parametric statistics.

Results

In line with our hypotheses, we detected a critical interaction: the difference in selection between the refutatory and the corroboratory version was greater in obsessive patients than in anxious patients (Mann–Whitney $U = 406$, $p < 0.001$, $\eta^2 = 1.1$).

As shown in **Table 1**, almost all the patients affected by OCD identified the refutatory vignettes as being more similar to the way they reasoned when worried. Moreover, their performance was at the ceiling of what was possible (98% of trials). However, they were unable to describe the indicators that they had used, and their judgments were quite rapid and intuitive. To further demonstrate that our obsessive patients identified with the refutatory vignettes more than they did with the corroboratory ones, for each patient and each pair of vignettes, we subtracted the rating they gave to the corroboratory vignette from the rating they gave to the refutatory one. We then computed a Wilcoxon test on the mean difference for each patient. In this way, we were able to confirm that the obsessive patients recognized refutatory vignettes as being more similar than corroboratory ones to their own reasoning (Wilcoxon, $z = 3.73$, $p < 0.001$, $\eta^2 = 0.08$). Males and females were similar in their performance (Mann–Whitney U = 18, *ns*). By contrast, patients affected by other anxiety disorders felt the vignettes with corroboratory reasoning to be more similar to their type of reasoning when worried in 95% of trials; this was considerably higher than by chance (binomial test, $p < 0.0001$). Also, this group of patients was unable to describe the cues that they had used, and again their judgments were quite rapid and intuitive. Applying a similar procedure to that used for the obsessive participants, for each anxious patient and for each pair of vignettes, we subtracted this time the rating of the refutatory vignette from the rating of the corroboratory one. We thus further demonstrated that these patients recognize corroboratory vignettes as closer to their way of reasoning than refutatory vignettes (Wilcoxon, $z = 3.95$, $p < 0.001$, $\eta^2 = 0.08$). No difference was found between the performance of male and female patients (Mann–Whitney U = 19, *ns*).

The vignettes were thus readily identifiable by both groups. This result supports the assertion of the theory that there are two characteristic ways of reasoning in patients. We therefore expected that OC patients and anxious patients would spontaneously reason in a refutatory and corroboratory form, respectively, during therapeutic sessions.

EXPERIMENT 2

This study examined the spontaneous reasoning of obsessive patients and other anxious patients during therapeutic sessions. Our theory predicted that obsessive patients would spontaneously use the refutatory strategy more often when

TABLE 1 | Percentages of refutatory and corroboratory vignettes that obsessional patients and anxious patients rated as more similar to their own reasoning (>3 on the Likert scale) in Experiment 1.

	Obsessive patients N = 18	Anxious patients N = 20
Refutatory versions (n = 6)	98%	55%
Corroboratory Versions (n = 6)	74%	95%

reasoning on topics typical of obsessions compared with when reasoning about other topics eliciting simply anxiety, e.g., work or relationships. In contrast, anxious patients should dominantly use the corroboratory strategy, both when reasoning about topics pertinent to their illness and when reasoning with other topics eliciting anxiety.

Method

Participants

The experiment tested two groups of patients: 12 obsessive patients (Male: 6; age: M = 34.8, SD = 10.9) and 10 patients affected by panic attack (Male: 6; age: M = 33.9, SD = 9.5). The two groups did not differ in age (Mann–Whitney U = 58.5, *ns*) or educational level (obsessive patients: M = 14 years, SD = 2.1, anxiety patients: M = 14 years, SD = 1.5, Mann–Whitney U = 68, *ns*). Both groups were undergoing treatment at the Centre for Cognitive Psychotherapy in Rome but were not on any psychopharmacological treatment. They were at the beginning of treatment and had been diagnosed using the Structured Clinical Interview and diagnosis for OCD and panic disorder in DSM-IV-TR (SCID; First et al., 1996).

Design, Materials, and Procedure

We asked two colleagues in Rome, who had been trained in cognitive psychotherapy but were blind to the hypothesis being tested, to conduct this experiment. We asked them to instruct all the patients to put into words, during two different therapeutic sessions (i.e., thinking aloud) their ruminations and thoughts on (1) a topic that was pertinent to their illness. For example, for an obsessive patient, an episode of possible contamination, and for an anxious patient, an episode in which he had to use the elevator and (2) on a topic that was not pertinent to their illness. For example, for all patients, episodes regarding general worries about money or their job. These two therapists were asked to help patients during the task by posing such questions as:

Put into words your thoughts while you are ruminating/thinking about the possibility of . . ..'

"How are you reasoning about it?"

"What are you telling yourself?"

"What thoughts are crossing your mind?"

The questions were the same for both the topics (pertinent topic vs. not pertinent topic to the illness). The patients were required to think aloud as they reasoned spontaneously while the therapist recorded what they said. The psychotherapists started to record audio the first time that a patient started to speak about a worry that crossed her/his mind. Two verbal reports were obtained from participants: one on a topic that was relevant to their condition, and the other on a non-relevant topic.

Two independent judges, both psychotherapists in Rome, who had also been trained in cognitive therapy and were blind to the hypothesis being tested, coded the pairs of recordings for the 22 patients. They were told to listen carefully as many times as they needed to in order to assign each recording to one of two mutually exclusive categories: patients using a refutatory reasoning strategy, and patients using a corroboratory reasoning strategy. They were given the following definitions of the two strategies:

- *Refutatory*: where the patient searches for counterexamples of the worst case under consideration.
- *Corroboratory*: where the patient searches only for examples of the worst case under consideration.

They also read two examples of each strategy, from two pairs of vignettes used in the earlier studies, each containing the same number of sentences. Where they disagreed in their judgments, which occurred in 3% of protocols, we asked a third judge (another psychotherapist in Rome) to make the final decision.

Results

Table 2 presents an example of the refutatory reasoning of an obsessive patient and an example of the corroboratory reasoning of an anxious patient, both for a topic that was relevant for their illness.

The Cohen's kappa correlation coefficients between the two judges for the two reasoning strategies (refutatory or corroboratory) were 0.83 for reasoning related to patients' illness and 0.65 for reasoning about other topics. Overall, Cohen's kappa for the reliability of their judgments was 0.73, which reflects a good agreement (Fleiss, 1981). For the few protocols on which they disagreed, the third judge cast the deciding vote.

TABLE 2 | Two typical protocols describing problems relevant to the patient's illness in Experiment 2, one from an obsessive patient using the refutatory strategy and one from an anxious patient using the corroboratory strategy.

Obsessive patient	Anxious patient
- I get off the bus, and I touch someone. I physically feel that my hand, or rather my fist, punched him. I think I hit him on the head. I think he could be dead. (*The patient focuses on his action, seeking to corroborate its negative consequences; he makes a transition to the emotion of guilt.)* I looked back, but the bus was already gone. I keep thinking about it. . . If I had hit him, he would have at least reacted, he would have called for help, he would have beaten me. (*He tries to infer counter-examples to the negative outcome of his having harmed the other person.*) Yes, but it all happened so fast. But people would have said something, they would have stopped me. *(He searches again for counter-examples to the negative outcome.)* What if no-one noticed it until it was too late? (*He thinks again of a corroboration.)*	I am always thinking that I could die. I imagine dying. (*Individual focuses on a danger that leads to intense anxiety in patients*). Yesterday, I remembered that my grandfather suffered from two heart attacks, and I often feel pain in my left arm. (*He searches for evidence confirming his hypothesis.*) Moreover, last week I moved, and so I have also carried many heavy boxes. I was very tired and stressed. I felt tachycardia, and my heartbeat so fast even when I was driving home. (*He searches for further corroboratory evidence.*) I know that my doctor thinks I'm exaggerating, but I couldn't ignore what I felt. I kept thinking: it could be a real heart attack this time. (*He continues to corroborate the hypothesis.*)

Comments in parentheses highlight the crucial cues to the strategy.

As shown in **Table 3**, obsessive patients tended to use a refutatory strategy and anxious patients tended to use a corroboratory strategy (Fisher–Yates exact test: $p < 0.05$, $\eta^2 = 0.05$) when they reasoned on a topic the was relevant for their illness. In contrast, when the two groups of patients thought about topics other than their illnesses, both of them tended to use the corroboratory strategy (Fisher–Yates exact test: $p > 0.5$).

EXPERIMENT 3

A number of studies have previously demonstrated that (hyper-) anxiety is responsible for the corroboratory pattern of reasoning (see de Jong et al., 1998). To date, no study has investigated the origin of the refutatory reasoning strategy in obsessive patients. In line with the hyper-emotion theory, with this study, we wanted to examine whether the latter form of reasoning actually stems from the (hyper-) guilt emotion. With this aim, we used two different vignettes: one in which the protagonist was guilty and responsible for the negative outcome (see below: vignette 1), and one in which a third person was responsible and guilty for the outcome (see below: vignette 2). According to the idea that obsessive symptomatology is based on the threat of being guilty, assessed as being imminent and the goal being to prevent it, we hypothesized that obsessive patients would use the refutatory strategy more than the Better Safe than Sorry (i.e., corroboratory) strategy, more so in scenarios in which they were guilty concerning a negative outcome (see vignette 1) than in scenarios in which others were guilty of the same outcome (see vignette 2, reported below), and more than patients suffering from other anxiety disorders.

Method

Participants

The experiment tested two groups of patients: 13 obsessive patients (Male: 8; age: $M = 33.5$, $SD = 7.7$) and 11 patients affected by panic attack (Male: 7; age: 32.6, $SD = 7.4$). The two groups were similar in age (Mann–Whitney $U = 66.5$, *ns*) and educational level (obsessive patients: $M = 14$ years, $SD = 2.1$, anxiety patients: $M = 14.8$ years, $SD = 1.7$, Mann–Whitney $U = 52$, *ns*). Both groups were undergoing treatment at the Centre for Cognitive Psychotherapy in Rome but were not on any psychopharmacological treatment. They were in the starting phase of treatment and had been diagnosed using the Structured Clinical Interview and diagnosis for OCD and panic disorder in DSM-IV-TR (SCID; First et al., 1996).

TABLE 3 | Frequencies of protocols reflecting a refutatory reasoning strategy and those reflecting a corroboratory reasoning strategy on a topic pertinent to the obsessive disturb or anxiety illness in Experiment 2.

	Relevant topics ($n = 22$)		Non-relevant topics ($n = 22$)	
	Refutatory strategies	Corroboratory strategy	Refutatory strategies	Corroboratory strategy
OC patients ($N = 12$)	10	2	1	11
Anxious patients ($N = 10$)	1	9	0	10

Design, Materials, and Procedure

To recruit these two groups of patients, at the end of the first session of their clinical assessment, patients were asked whether they wanted to take part in a study on the way people reason about certain crucial topics. They were told that there were no right or wrong answers and that we were only interested in their opinions. Four colleagues in Rome and in Palermo, who had been trained in cognitive psychotherapy and who were blind to the hypothesis being tested, were asked to carry out the experiment. Patients were instructed to read two short vignettes, each leading to a negative outcome: one described a situation in which the protagonist of the story could be responsible or guilty for the negative outcome, while in the other, the possible culprit was a third person. They were then asked to reason about both stories, writing down their thoughts in order to reassure themselves beyond any reasonable doubt about the negative outcome.

The story concerning the culpability of the protagonist was, for example (vignette 1):

> *Imagine that it's Sunday afternoon and I'm with my niece. I'm playing with her on the sofa when my nose starts itching, and I sneeze. I don't care and keep on playing with her. Later, it strikes me that my niece might be sick because of my sneeze. It would be because of my carelessness. I should have been more careful.*

The story concerning the culpability of a third person was, for example (vignette 2):

> *Imagine that I take my niece to the kindergarten. I see her playing with other kids and the teacher. As I approach them, the teacher's nose starts itching, and she sneezes several times. She doesn't care and keeps on playing with my niece. Later, it strikes me that my niece might be sick because of her teacher's sneeze. It would be because of her carelessness. She should have been more careful.*

After having read each story, all participants were told:

> *Try to reassure yourself about this possibility, beyond any reasonable doubt. Write all the thoughts that come into your mind.*

The participants in each group read the two stories in a different random order and in two different therapeutic sessions.

Two independent judges, both psychotherapists in Palermo who were blind to the hypothesis being tested, categorized the two protocols from each participant in terms of whether they exhibited a refutatory or a corroboratory reasoning strategy (see Study 2 for their instructions). Where they disagreed on their judgments, a third judge (another psychotherapist in Palermo) cast the deciding vote.

Results

Table 4 shows two typical protocols of the two sorts of reasoning from two representative obsessive patients. Agreement

TABLE 4 | Two typical protocols of the two sorts of reasoning from two representative obsessive patients, reasoning about the story eliciting guilt (refutatory strategy) and the story describing another's guilt (corroboratory strategy) in Experiment 3.

Refutatory strategy for story eliciting protagonist's guilt	Corroboratory strategy for story describing other's guilt
– Surely it doesn't depend on that, but if I had a cold, it is. The mere fact that I sneezed made the air full of germs. (*The participant corroborates the negative outcome.)* – Maybe the window was open. If so, the germs could have gone out (*to refute the negative outcome*). – Nevertheless, they could have contaminated the kid; they could have been everywhere in the air (*to corroborate the negative outcome*). – Surely it was a coincidence. Maybe she already had a cold (*a refutation).* – But what if this is not the case? (*A corroboration.*)	The teacher had a cold, and she sneezed. So, the probability that she contaminated my niece is very high. *(The participant corroborates the negative outcome.)* Moreover, she was playing with the kid *(a corroboration).* So, the air was contaminated. I cannot see how it could not have been contaminated, although they were in the playground *(a corroboration).* Moreover, they were so close *(a corroboration).* So, if my niece fell ill, she was truly contaminated by the sneezes *(a corroboration).*

Comments in parentheses highlight the crucial cues to the strategy.

between the two judges regarding the two forms of reasoning (corroboratory vs. refutatory) was 0.73 for the stories concerning the protagonist's guilt and 0.83 for the stories concerning another person's guilt (Cohen's kappa = 0.78). They disagreed on only four protocols.

As shown in **Table 5**, obsessive patients were prone to use a refutatory strategy with a story concerning their own guilt more than were anxious patients (Fisher–Yates exact test: $p < 0.05$, $\eta^2 = 0.04$), while, with the story describing another person's guilt, they tended to reason in a corroboratory way, as did the anxious patients (Fisher–Yates exact test: $p > 0.5$).

DISCUSSION

With our studies, we have demonstrated that individuals affected by psychological disorders produce characteristic reasoning strategies that depend on the hyper-emotion elicited by a threat. In particular, in our first study, we showed the ability of anxious patients and obsessive patients to recognize the refutatory and the corroboratory patterns of reasoning, respectively, as more similar to their own, regardless of the content of the inference. In the second study, we further demonstrated that obsessive patients spontaneously produced the refutatory pattern of reasoning, while other anxious patients produced the corroboratory pattern when thinking about topics that were condition-relevant. Finally, in accordance with hyper-emotion theory (Johnson-Laird et al., 2006), we showed that corroboratory reasoning was elicited by anxiety, while a refutatory form of reasoning stemmed from the (hyper-) guilt emotion (Experiment 3). The former result is in line with the wider literature showing that, in the face of exposure to a threat eliciting anxiety, individuals suffering from hypochondria or other anxiety disorders are inclined to focus on the danger and to search for examples confirming it (e.g., de Jong et al., 1998; Gilbert, 1998).

TABLE 5 | Frequencies of protocols reflecting a refutatory reasoning strategy and those reflecting a corroboratory strategy in obsessive and anxious patients trying to refute the outcome that the protagonist in the story might be guilty in Experiment 3.

	Story eliciting protagonist's guilt		Story describing another's guilt	
	Refutatory strategy	Corroboratory strategy	Refutatory strategy	Corroboratory strategy
Obsessive patients (*N* = 13)	12	1	2	11
Anxious patients (*N* = 11)	4	7	1	10

The latter finding is significant because, as anticipated above, no other study has investigated either the refutatory form of reasoning or its origin in obsessive patients, except for the study by Giele et al. (2011). The obsessive-like step-by-step reasoning is the only example of a strategy that is comparable to our refutatory pattern of reasoning. It is worth noting that both their and our studies demonstrate that this form of reasoning has a paradoxical effect. The obsessive-like creation of small steps leading from an innocuous situation to a catastrophic consequence increases the plausibility of the feared outcome, potentially maintaining the obsessive condition. Such reasoning begins with thoughts about the possible danger (Johnson-Laird et al., 2006), whereby patients try to defend against this possible danger and attempt to consider the situation in a comprehensive way. As a consequence, the obsessive patient begins to make a series of steps toward this self-created danger. However, this strategy has the ironic effect of strengthening the belief that the feared event will actually happen. Our findings appear to add to the growing list of studies showing that the effects of reasoning in psychological disorders run counter to the real intentions of patients: the safety strategies used by patients are counterproductive and lead to a decrease, instead of an increase, in confidence that there will be no negative outcome.

Limitations and Future Research

Our studies have several limitations. Although our aim was to investigate the reasoning strategies of patients affected by certain psychological disorders, one limitation is that we did not have any healthy control group. Therefore, future studies should investigate what style of reasoning non-clinical individuals use or what style of reasoning, if any, they recognize as being their style.

A second limitation, again pertaining to all of our studies, is that we did not include at least a clinical control group characterized by an emotion other than either anxiety or

guilt – for example, depressed people with sadness. Hyper-emotion theory (e.g., Johnson-Laird et al., 2006) predicts that the reasoning strategy of depressed people will be different from the two groups analyzed in this paper. Such individuals pay particular attention to a person or situation assessed as being lost, and they feel intense sadness about this. Individuals attempt to infer the more positive conclusion that the loss is not permanent (positive hypothesis) and try to corroborate it. But the more they pay attention to the lost person or entity, the higher their standards for what would be acceptable as a substitute are set. As a consequence, they infer that the loss is irreplaceable (falsifying the positive hypothesis) (see also Mancini and Gangemi, 2015). According to this, we could expect that depressed patients would recognize neither of our two reasoning strategies (corroboratory and refutatory) as similar to their own and would reason in a different way. Future studies should thus investigate other styles of reasoning, in order to verify whether and how changing the emotion changes the reasoning strategy as well.

A third critique is pertinent to Experiment 3, specifically. Here, we used the same experimental procedure we had used in earlier experiments (see Johnson-Laird et al., 2006; Gangemi et al., 2013), where we asked participants to read stories whose contents were designed to elicit guilt in the protagonist. Skeptics may argue that how emotions explain reasoning in such an experiment is something of a mystery. However, hyper-emotion theory does propose an explanation. It states that emotions stimulated by the topic of the story (the guilt of the protagonist vs. the guilt of other persons) lead individuals to be motivated to reason in a way pertinent to their source in order to reassure themselves about the damage. This effect, together with the standard inferential ability, yields the pattern of inferences in our experiment. However, future studies should further verify whether guilt actually elicits the refutatory strategy and anxiety elicits the corroboratory strategy in this study, for example, by assessing the level of both the emotions before and after having read each story with a manipulation check questionnaire.

Clinical Implications

This study may have some clinical implications. In general, if hyper-emotion theory is correct, then there are transitions from normal life emotions to abnormal ones in psychological disorders. Therefore the therapeutic goal should have as its focus the disengagement of these transitions and of patterns of inference that would otherwise boost the aberrant emotions. For example, it appears that when patients acquire the ability to accept the possibility of being guilty, there is a decrease in obsessive symptoms, even when guilt acceptance is not related to the patient's symptomatic domain (Cosentino et al., 2012). Moreover, it is common for patients to experience a feared situation, quickly imagine a catastrophic outcome, and to be engaged in one of the two forms of reasoning. A sort of meta-cognitive intervention focused on leading patients to become aware of the way they reason on the disorder-related threat could be very helpful. Explaining, for example, that the refutatory reasoning in the case of catastrophes feared by OCD subjects will be counterproductive may actually be effective.

Finally, in certain cases, the steps leading from a neutral situation to a catastrophic outcome are not properly elaborated by the anxious or obsessive patient or may appear particularly implausible to the therapist. Therapists might, in such cases, attempt to test these catastrophic scenarios by asking how exactly the patient imagines that the particular transitions could take place (e.g., "how exactly might HIV be transmitted from the door to the hat?") Such therapeutic intervention may be risky, in the sense that it could foster the process that is examined in this paper: it may paradoxically increase the plausibility of the feared outcome.

CONCLUSION

In sum, patients develop characteristic strategies of reasoning that depend on the (hyper-) emotion elicited by the threat: anxious patients make corroboratory inferences, adducing only evidence that confirms the risk (*corroboratory strategy*), while obsessive patients make refutatory inferences, adducing counter-examples disconfirming the risk (*refutatory strategy*). There is a paradoxical effect of these reasoning strategies that contributes to the maintenance of psychological disorders, systematically leading to the confirmation of the dysfunctional beliefs that are central to these illnesses.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Associazione di Psicoterapia Cognitiva, Rome, Italy. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AG and FM conceived and designed the experiments and analyzed the data. AG and KT collected the data. AG, FM, and KT wrote the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.02335/full#supplementary-material

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METHODS
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Burnout, Job Dissatisfaction, and Mental Health Outcomes Among Medical Students and Health Care Professionals at a Tertiary Care Hospital in Pakistan: Protocol for a Multi-Center Cross-Sectional Study

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Burnout, a state of vital exhaustion, has frequently been related to work-related stress and job dissatisfaction. Given the emotionally and physically challenging nature of their work, high rates of burnout have been reported among health care professionals. This may put them at a higher risk for of suffering from adverse mental health outcomes, including depression, anxiety and stress. In our study, we aim to assess the prevalence i of and associations among burnout and job dissatisfaction and adverse mental health outcomes in a developing country, where the challenges faced by the health care system are unique. Facilities are over-burdened and there is a sharp contrast between doctor to patient ratios in developing and developed countries. We plan to conduct a cross sectional study at the largest tertiary care hospital in Pakistan and its peripheral affiliated health centers. A proportionate sampling technique will be employed to include medical and nursing students, interns, residents and consultants. Previously validated questionnaires, including the Maslach Burnout tool, DASS 21, and Job Satisfaction Survey will be disseminated through Survey Monkey. Statistical analysis will be conducted using IBM SPSS Statistics Version 23 to study the association among burnout, job dissatisfaction, adverse health outcomes and demographic and work-related factors This study may begin laying the foundation for prioritizing the novel concept of physician mental health in the developing world. Further research building on to the results of this study will generate evidence to make recommendations about routine screening for mental illness and policy changes in the health care system.

Keywords: burnout, depression, stress, anxiety, job satisfaction, health care professionals, physicians, doctors

Abbreviations: AKUH, Aga Khan University Hospital; DASS-21, depression anxiety stress scale 21; DP, depersonalization; EE, emotional exhaustion; ERC, ethical review committee; IQR, inter quartile range; JSS, job satisfaction survey; MB tool, Maslach burnout tool; MLR, multiple linear regression; PA, personal accomplishment.

INTRODUCTION

The term "Burnout" was first coined in the 1970s by an American psychologist, Herbertt Freudenberger (InformedHealth.org [Internet], 2006). Since then, over 6000 pieces of literature encompassing the concept of burnout have been published but no unified definition or diagnostic criteria has been established (Schaufeli et al., 2009). The ICD-10 now codes burnout as "a state of vital exhaustion," affecting both mind and body and includes several elements in common with depression and neglect of physical health (inadequate sleep, lack of exercise, imbalanced diet) (Schaufeli et al., 2009; Korczak et al., 2010; Kaschka et al., 2011; Drummond, 2015; Melnick and Powsner, 2016; Schonfeld and Bianchi, 2016). According to the conservation theory, a state of burnout occurs when an individual's abilities to cope with physical and emotional stressors are depleted (Hobfoll, 2001; Lesser et al., 2010). While countless physical and emotional stressors may challenge an individual, work-related stress, particularly job dissatisfaction, has often been linked to burnout states (Griffin et al., 2009; Zhou et al., 2017).

Health care provision is a challenging and stressful profession (Ramirez et al., 1996; Familoni, 2008). The serious nature of the work leaves little margin for error (Familoni, 2008). Health care professionals may experience Job dissatisfaction from a failure to cope with competitive work environments, long work hours coupled with overtime and an encroachment on personal life by the psychological burden associated with ethical dilemmas and decision making for patients (Cooper et al., 1989; Theorell et al., 1990; Sutherland and Cooper, 1993; Enzer and Sibbald, 1999; Coomber et al., 2002). Given the emotionally and physically challenging nature of their work, the rates of burnout are alarmingly high in health care professionals, with previous studies reporting rates as high as 54.3% in professionals and 45% in medical students (Bauer et al., 2006; Dyrbye et al., 2014; Lee et al., 2015). In 2019, a meta-analysis on results from 22,778 residents showed that one out of every two residents have suffered from burnout (Low et al., 2019).

Adverse mental health outcomes have been linked to prolonged states of burnout, including depression, anxiety and stress (Prosser et al., 1996; Turnipseed, 1998; Bennett et al., 2005; Peterson et al., 2008). Frequent burnout makes health care professionals more susceptible to a variety of mental illnesses with physical manifestations such as anxiety, depression, insomnia, fatigue, and lethargy (Welp et al., 2015). Depletion of coping abilities may even lead to the development of unhealthy coping strategies, including substance abuse and suicide (Sonneck and Wagner, 1996; Riley, 2004).

Not only do such high levels of stress adversely affect the health and emotional well-being of doctors, they are a direct threat to the quality of care that doctors can provide to their patients While concern for the health of professional caregivers is paramount, such high rates of burnout are a direct threat to the quality of care doctors can provide for their patients (Felton, 1998). Some consequences include early retirements, an increased number of sick leaves from work and reduced daily productivity compromising the delivery of empathy enriched "professional responsibility" by doctors (Lesser et al., 2010; Kumar, 2016). Indeed, higher mortality ratios have been reported in departments with higher burnout rates (Welp et al., 2015).

Study Aims

While several studies have been conducted to investigate occupational stressors, job satisfaction, burnout and effects on mental health among health care professionals in developed countries (Sonneck and Wagner, 1996; Shapiro et al., 2005; Rössler, 2012), few studies have focused on the developing world where pressures on the health care system are unique. Facilities are over-burdened the doctor to patient ratios are in sharp contrast to the developed world (World Health Organization [WHO], 2013; Khalid and Abbasi, 2018). In 2013, a study conducted in Pakistan reported a rate of 74% among medical and surgical residents (Zubairi and Noordin, 2016).

Primary Aim

To study the associations among burnout, job dissatisfaction and mental health outcomes in medical students, interns, residents, fellows and attendings at a tertiary care hospital its peripheral affiliated centers in Pakistan.

Secondary Aims

1. To determine the prevalence of job dissatisfaction amongst health care professionals in a tertiary care hospital and its peripheral affiliated centers in Pakistan.
2. To determine the prevalence of burnout amongst health care professionals in a tertiary care hospital and its peripheral branches in Pakistan.
3. Identify the key stressors which are associated with job dissatisfaction amongst health care professionals in a tertiary care hospital and its peripheral branches in Pakistan.

Our study attempts to identify the factors which may be associated with burnout, job dissatisfaction and adverse mental outcomes (**Figure 1**) so that targeted interventions can be made. The results of this study will be beneficial for improving physician and ultimately patient health. The conduction of a study encompassing the topic of physician mental health is among the novel concepts in low middle income countries. If results are favorable, it has potential to scale up to becoming grounds for routine screening and possibly policy changes in the health care system.

METHODS AND ANALYSIS

Study Design

This is a cross sectional study to conducted over a period of 4 months (July 2019–November 2019).

Study Site

The study will be conducted at the Aga Khan University Hospital and its peripheral affiliated centers including Sultanabad AKU Medical Centre, Metroville Medical Centre and AKU for Women Garden East.

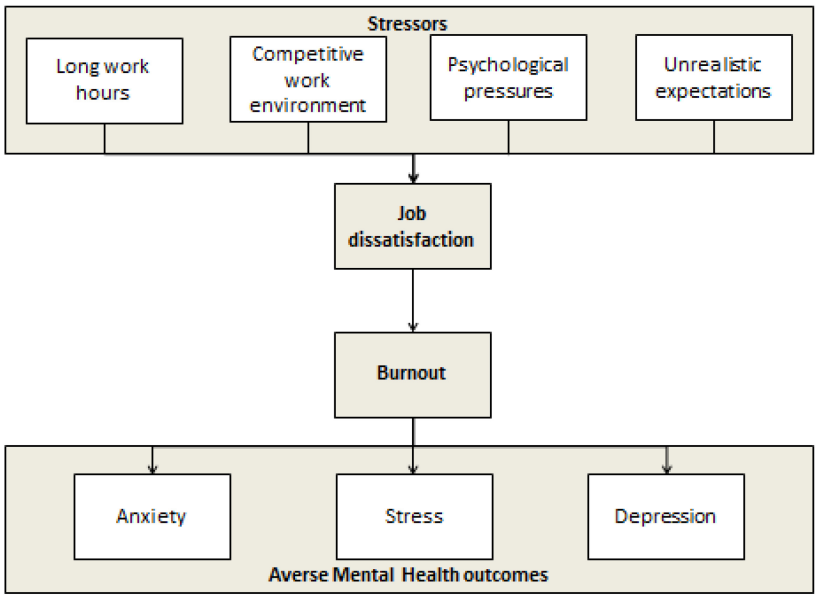

FIGURE 1 | Associations among work-stressors, job dissatisfaction, burnout, and mental health.

Participants

Inclusion Criteria

1. Students enrolled in the Aga Khan University and medical college (years 1–5).
2. Students enrolled in the Aga Khan school of nursing (years 1–4).
3. Interns employed at Aga Khan University Hospital (1 year contract employees).
4. Residents and attending faculty from Internal Medicine, Emergency medicine, Pediatrics, Surgery, Psychiatry, Neurology, Ophthalmology, Orthopedics, Obstetrics and gynecology, Family medicine and all related specialties employed at AKUH and its peripheral branches.

Exclusion Criteria

1. Individuals who do not consent.
2. Students, interns or residents who are on visiting elective rotations at AKUH.

Sampling Technique and Size

Total population sampling, a subtype of purposive sampling, will be employed. Sample size was calculated using open Epi software version 3.01. Using a level of significance of 5%, precision of 2.5%, design effect of 1, and prevalence of mental health outcomes (depression, anxiety and stress) among students, residents, interns and faculties ranging from 7.9 to 44% (Jadoon et al., 2010; Henning et al., 2014; Washdev et al., 2017; Yahaya et al., 2018), a minimum sample size of 1669 will be needed, with 348 medical students, 348 nursing students, 56 interns, 347 residents, 35 fellows, and 535 faculty members. To account for a response rate less than 100% and limited study duration, questionnaires will be disseminated to all individuals satisfying the eligibility criteria, totaling 2398 health care professionals.

Data Gathering

Procedure

The questionnaires will be disseminated using survey monkey which will utilize electronic consent. The questionnaires are will be provided to the participants in the English Language. There is no need for translation into the local language as all potential participants are fluent in English.

Tools

Three questionnaires will be used:

1. *DASS 21* comprises of 21 questions related to symptoms of stress, depression and anxiety. This questionnaire has a sensitivity and specificity of 57 and 76% respectively for depression and 86 and 64% respectively for anxiety (Mitchell et al., 2008). It is estimated to be completed in 6–7 min. The DASS 21 has been used previously in Pakistan, with Chronbach alpha scores of 0.91, 0.84, and 0.90 for depression, anxiety and stress, respectively (Ashiq et al., 2016; Kumar et al., 2019).
2. *Maslach burnout tool* has three sub-scales: EE, DP, and PA. It has a total of 22 questions and will take approximately 6 min to complete. In 2013, Kleijweg et al. (2013) reported the sensitivity and specificity of the MB tool to be 78 and 48% respectively. This tool has frequently been used to assess burnout amongst medical students, doctors and residents in various studies (McManus et al., 2004; Dyrbye et al., 2010). This tool has also been used previously in Pakistan with Chronbach alpha coefficients reported to be 0.75, 0.74, 0.65 for EE, DP and lack of accomplishment, respectively (Abbas et al., 2012; Ali and Ali, 2014; Zubairi and Noordin, 2016).

3. *Job Satisfaction Survey*, developed by PE Spector (1985), has 31 questions and will take approximately 7 min to complete. The test–retest value for this survey is reported to be 0.80–0.64 and the convergent value for contruct validity has been reported to be 0.76 (Koeske et al., 1994). The Cronbach's alpha for the use of JSS in Pakistan has been reported to be 0.78 (Ali and Ali, 2014; Zubairi and Noordin, 2016).

The JSS and DASS-21 have been used together in several studies (Henning et al., 2014; Sasidharan and Kolasani, 2016).

Variables, Operational, and Outcome Definitions

Independent (Exposure) Variables

Demographic

Participants will be requested to fill out a *pro forma* with basic demographic variables including age, gender, marital status, designation, specialty and duration of work/study (**Supplementary Appendix 1**).

Job satisfaction

Job satisfaction is the conglomerate of feelings and beliefs that people have about their current job. A persons' job satisfaction can range from extreme satisfaction to extreme dissatisfaction (George and Jones, 2008). For assessing the job satisfaction, the sum of the 36-point questionnaire, with each response ranging from 1 to 6, will be calculated and divided into three quartiles (<25, 25–75, >75). All individuals falling in the >75% quartile will be considered as having poor job satisfaction (**Supplementary Appendix 2**).

Burnout

For assessing burnout, we will use the MB tool. Burnout is defined as a state of emotional and physical exhaustion caused by a prolonged period of stress and frustration (Maslach et al., 1996). Responses ranged between 0 and 3 describe severity of burnout. MB tool scores output in three dimensions – EE, DP, and PA, which will be transformed into dummy categorical variables using the cutoff values for doctors, as recommended by Maslach et al. (1986).

Dependent (Outcome) Variables

Depression

Depression is an illness that is marked by feelings of sadness, worthlessness, or hopelessness, as well as with problems concentrating and remembering details. For the assessment of depression and anxiety, we will use the questionnaire, DASS-21by Henry (Henry and Crawford, 2005). The DASS-21 is a 4 point questionnaire with severity scores ranging from (InformedHealth.org [Internet], 2006; Schaufeli et al., 2009; Melnick and Powsner, 2016; Schonfeld and Bianchi, 2016) and severity is rated using the sum of responses to the 21 questions (**Table 1** and **Supplementary Appendices 3**, **4**).

TABLE 1 | DASS severity rating (multiply summed score by × 2) (Henry and Crawford, 2005).

Severity	Depression	Anxiety	Stress
Normal	0–9	0–7	0–14
Mild	10–13	8–9	15–18
Moderate	14–20	10–14	19–25
Severe	21–27	15–19	26–33
Extremely severe	28+	20+	34+

Anxiety

Anxiety is a feeling of fear or apprehension about what is to come (Wurman et al., 2001). A score greater than 20 in the DASS-21 will be interpreted as anxiety.

Stress

A score of greater than 34 in the DASS-21 will be interpreted as stress.

Data Management

Only the primary investigator and data analyst will have access to the electronic data which will be kept in a password protected database.

Statistical Analysis Plan

This is an observation, cross-sectional study to estimate the prevalence of burnout, job dissatisfaction and adverse health outcomes amongst health care professionals and assess associations among them and with other potential demographic factors.

Analysis will be performed using IBM SPSS Statistics version 23. Descriptive statistics will be applied to categorical variables as frequencies or proportions and as measures of central tendency to quantitative variables [mean ± SD or Median (IQR) as appropriate]. Mean scores will be reported for depression, anxiety and stress. One way ANOVA/Kruskil Wallis test will be used to compare differences amongst scores of medical students, interns, residents and faculty different groups. In order to assess the relationship between depression, anxiety and stress correlation analysis will also be performed using Pearson or Spearman rank correlation coefficients as appropriate. Univariate and MLR will be performed to evaluate the effect of independent variables (age, gender, marital status and designation) on the outcomes. Adjusted β-coefficients with their 95% CI will be reported. A p-value of <0.05 will be considered statistically significant. The results of this study will be depicted in the dummy tables and graphs as shown in **Supplementary Appendix 5**.

Caveats and Potential Pitfalls

The study is limited to a single city and affiliated hospitals of a single institute and may not be a reflection of the entire Pakistani population. For this reason, this study must be replicated in smaller cities across several hospitals to improve generalizability. Furthermore, due to time constrains of health care workers, filling in a questionnaire with over 50 questions may limit response rates. In response rates are too low to meet the minimum sample size, the designated study duration can be extended and frequent reminders can be sent to participants through Survey Monkey. Lastly, our study is a pilot study which will only be studying associations among burnout, job dissatisfaction and adverse mental outcomes. To establish a stronger statistical relationships,

long term cohort studies with adequate control of confounders need to be conducted.

Ethics and Dissemination

The Ethical approval for this study has been obtained from the institutional review board of the Aga Khan University (ERC number: 2019-1126-3077). Electronic consent form will be obtained from each participant through Survey Monkey prior to the study. A unique study identification number will be assigned to each participant. Permissions from the authors of the DASS-21 questionnaire and the JSS questionnaire have been taken to conduct our study using their questionnaires. MBI-Burnout tool will be purchased from the Consulting Psychologists Press[1].

Implications for Patients

It will be a cross sectional study design where participants will answer questionnaires regarding job satisfaction, burnout and mental health. The participants will be health care professionals and there will be no direct involvement of patients. Long term, however, addressing physician burnout may improve quality of health care provided to patients. The study findings will be disseminated through the university newsletter and mental health conferences following its publication in a national or international journal. Participants who wish to see their results will receive their report via email.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

[1] http://www.mindgarden.com/products/mbi.htm

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, The Aga Khan University Hospital, Karachi (ERC: 2019-1126-3077). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SM: study design and protocol writing. AN: protocol writing. NQ: study design and protocol review. ZA: study design. NZ: protocol review. RL and SN: protocol review and supervisor. All authors contributed to manuscript revision, and read and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2019.02552/full#supplementary-material

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OPINION
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Common Psychological Factors in Chronic Diseases

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The construct of "*chronic physical diseases*" (CPDs) encompasses a number of heterogeneous conditions that have persisting lifelong effects on the quality of life (QoL) and subjective well-being (Sprangers et al., 2000). According to epidemiological studies, CPDs are constantly increasing, not only in Western countries but also in developing/emerging countries, with certain prevalent differences regarding CPD type (Vos et al., 2016), raising questions on the multifactorial genesis of this phenomenon. The role of psychiatric disorders is, for example, well-known as comorbid conditions able to affect the course of CPD with a number of *sequelae* and complications (Daré et al., 2019).

The most common CPDs (namely, cardiovascular disease, diabetes mellitus, neoplastic diseases, asthma, arthritis, and osteoporosis) are often complicated by psychiatric symptoms or emotional/psychological subjective suffering (Martino G. et al., 2019; Rosa et al., 2019), a datum that underlines the close correlation that exists between such conditions. However, the relationships and the mutual influences between CPD and psychopathological manifestations are far from established (Marchini et al., 2018; Miniati et al., 2018; Martino G. et al., 2019).

Findings on psychological/psychopathological dimensions in patients with CPD, both from a cross-sectional and from a lifetime perspective, are available in the literature, with an emphasis on their impact on cognitive functioning, emotional processing, exposition to stressful events (SLEs) and adversities, medical and psychological outcomes, and combined interventions and therapies (Bernard et al., 2018; McGilton et al., 2018; Shao et al., 2019). A number of studies have, for instance, already explored the impact of signs and symptoms belonging to the realm of psychopathological disorders on the most common CPDs, with a measure of the subjective perception of well-being and QoL (Megari, 2013). More specifically, alexithymia, anxiety, depression, psychological distress, sleep quality, and emotional dysregulations have been systematically assessed in patients with fibromyalgia, Type 2 diabetes, psoriasis, and osteoporosis (Palagini et al., 2016; Catalano et al., 2018; Martino et al., 2018a,b; Cristina et al., 2019; Kelly et al., 2019; Marchi et al., 2019; Martino M. L. et al., 2019; Settineri et al., 2019a,b). This datum represents the increasing tendency of the scientific community to take an interest in the aforementioned connection between the psychological and physical spheres, hypothesizing a positive correlation between the two, where a higher psychological and QoL malaise correspond to the increasing severity of the pathology.

In nearly all of the abovementioned conditions, cognitive functioning and performances were impaired, as enhanced by studies with cognitive tasks, again raising questions as to the different weight and role of metabolic dysregulations vs. comorbid anxiety or depressive disorders in determining the severity of cognitive dysfunctions (Guicciardi et al., 2019).For example, emotional processing and depression has been found to enhance "*pain catastrophization*," which could be described as the cognitive attitude of interpreting the experience of pain in an excessively negative manner, during upper endoscopy in young, especially female, patients, when exposed for the first time to diagnostic procedures and pain therapies (Sullivan et al., 2001; Lauriola et al., 2019). A number of studies also highlight the reciprocal influences between psychological and medical conditions in affecting cognitive performances and emotional reactions among children and young adults, with relevant *sequelae* in adulthood and in the elderly, while other studies have

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opened up debate on the interaction of age, gender, and medical conditions on mental status (see the association between early childhood SLEs, depression, cognitive functioning, and lipids' metabolism alterations; Stewart et al., 2000; Péterfalvi et al., 2019). Other studies demonstrate how an early diagnosis of a neuropsychiatric condition (such as ADHD) may change the electrophysiological characteristics and the overall subjective neuropsychological profile during adulthood (Angela et al., 2018; Klein et al., 2019), as possibly determined by the occurrence of manic symptoms and PTSD in young adults (Dell'Osso et al., 2014) or the emotional suppression or oneiric perturbation in subjects affected by psychosomatic illnesses (Settineri et al., 2019a,b).

Overall, these studies demonstrate the importance of a multidisciplinary approach in treating patients affected by CPD and both psychological and psychopathological disorders. Both psychological and physical interventions in patients with CPD could ameliorate prognosis, considering the described relationships between psychological factors and CPD, as identified by studies on the positive impact of a healthy psychological functioning on CPD (Schiavon et al., 2017; Gentili et al., 2019). Psycho-educational interventions, mindfulness-based cognitive therapy, non-invasive brain stimulation techniques, peer-to-peer supports, and a health-based approach have been all tested with promising results in patients with CPD (Castelnuovo et al., 2015; De Jong et al., 2016; Naro et al., 2016; Callus and Pravettoni, 2018; Conversano et al., 2019).

In conclusion, it could be inferred that the bidirectional association between CPD and psychopathological factors might lead to an exacerbation of both conditions, with mechanisms that are only partially known and described. However, a relevant corpus of knowledge supports the need for an integrated approach (physical, psychological, and psychopathological) that takes into account the subjective experience of the single patient from a lifetime perspective. As a consequence, it is necessary to consider the corollary of symptoms that the patient who suffers from a chronic disorder manifests as a unitary corpus, where it is possible to intervene both with medical and psychological science to improve QoL and therefore physical symptoms. In the history of the patient's illness, the weight of psychological variables plays a fundamental and non-negligible role when the doctor's interest is that of treating the patient from a long-term perspective.

The development of therapeutic interventions able to fuse different perspectives into a tailor-made interdisciplinary management approach in a single patient and the development of a quality body of research on the topic are future challenges in order to improve QoL and the subjective well-being of patients with CPD and psychopathological signs and symptoms.

AUTHOR CONTRIBUTIONS

CC was responsible for writing the entire opinion article, for checking the adequacy of references and of all aspects of layout.

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Longitudinal Profiles of Psychological Well-Being and Health: Findings From Japan

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Studies have reported relationships between psychological well-being and physical health in Western cultural contexts. However, longitudinal associations between well-being and health have not been examined in other cultures where different values and beliefs about well-being exist. This paper examined whether longitudinal profiles of well-being predict prospective health among Japanese adults. Data came from 654 people who completed two waves of the Midlife in Japan (MIDJA) Study collected 4–5 years apart. Health outcomes were assessed with subjective health, chronic conditions, physical symptoms, and functional health. The results showed that persistently high well-being predicted better health over time. High-arousal positive affect, which is relatively less valued in Japanese culture, was also associated with better health. The findings add cross-cultural evidence to the cross-time link between well-being and health.

Keywords: well-being, longitudinal, culture, protective factors, physical symptoms, chronic illness, healthy functioning

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INTRODUCTION

Psychological well-being is multifaceted including both eudaimonic (e.g., purpose, fulfillment) and hedonic (e.g., feeling good) aspects. Psychological well-being has been shown to predict a wide array of health outcomes such as better subjective health (Benyamini et al., 2000), fewer chronic conditions (Friedman and Ryff, 2012), and lower rates of mortality (Boyle et al., 2009; Diener and Chan, 2011). Most prior findings have, however, been based on cross-sectional data, making the causal nature of the relationships unclear. The limited number of studies using longitudinal data have shown that higher levels of purpose in life, a component of psychological well-being, predicts future health outcomes, after controlling for baseline health (e.g., Boyle et al., 2009; Kim et al., 2013). In addition, cumulative profiles of well-being focused on comparisons between persistently high or low levels of well-being predict better cross-time health, measured in terms of subjective health, chronic conditions, and functional impairment (Ryff et al., 2015).

Notably missing in this literature is research from non-Western cultural contexts. This omission is important because psychological well-being is known to be shaped by cultural values and beliefs (Kitayama et al., 2000; Kitayama and Park, 2007; Fulmer et al., 2010; Karasawa et al., 2011; Ryff et al., 2014; Miyamoto et al., 2019). Thus, it is unknown whether distinct aspects of well-being benefit health in different cultural contexts. To address this issue, the current study examined longitudinal links between diverse indicators of well-being and self-reported health in Japan, using assessments comparable to a prior study in the United States (Ryff et al., 2015; Radler et al., 2018). Japan is a

relevant comparison because it is comparable to advanced Western countries in modern lifestyles and economic development, but also encompasses substantial differences in conceptions of self and relationships with others (Markus and Kitayama, 1991).

Although some dimensions of well-being have been considered important in both Japan and Western countries, other dimensions are thought to be particularly important in Western cultural contexts but less relevant to Japanese (Kitayama et al., 2000; Tsai, 2017). For example, there are notable parallels between purpose in life, an aspect of well-being in the West that has increasingly been linked to positive health outcomes (e.g., Boyle et al., 2009; Kim et al., 2013; Hill and Turiano, 2014) and the Japanese concept of *ikigai*, which refers to what makes life worth living. *Ikigai* is believed to be the most common indicator of psychological well-being in Japanese culture (Nakanishi, 1999). Kumano's (2017) content analysis of how Japanese define *ikigai* in everyday language further showed that the concept comprises a sense of accomplishment, devotion (despite difficulties), and social and benevolent contribution. These elaborated ideas suggest possible overlap with other aspects of well-being such as personal growth and positive relations with others[1]. Pertinent to health, *ikigai* has repeatedly predicted better health in Japan, including lower mortality and incidence of functional disability (Sone et al., 2008; Tanno et al., 2009) and greater physical activity (Ueshima et al., 2010).

In contrast, other aspects of well-being have shown differences in cultural values and meanings. Two examples include autonomy and positive affect, particularly high-arousal positive affect (e.g., excited, enthusiastic). Individuals in Western cultures tend to experience self as an independent entity from their social surroundings, whereas self-concept in East Asian cultures is defined via one's interdependent relations to other people (Markus and Kitayama, 1991). Within the interdependent conception of self, attuning and adjusting to others is crucial to social functioning and individual well-being (Kitayama and Markus, 2000). Thus, autonomy, defined as a commitment to following individual convictions and beliefs may be contrary to virtuous living in Japanese compared to Western cultural contexts (Oishi, 2000; Karasawa et al., 2011). Similarly, high-arousal positive affect is considered less desirable in East Asian cultures because it may interfere with fulfilling cultural expectations, such as vigilant attunement to social demands and corresponding adjustment (Tsai et al., 2007). Such a view contrasts with Western formulations wherein high-arousal positive affect (e.g., excitement) is central to hedonic well-being (Tsai et al., 2006; Uchida and Kitayama, 2009). Thus, autonomy and high-arousal positive affect may not be strong predictors of health, including its improvement across time, in Japan.

Such thinking converges with prior work showing cultural differences in associations between autonomy and positive affect with health. Kitayama et al. (2010) found that personal control, which is conceptually similar to autonomy, was positively related to self-rated health among both Japanese and United States adults, but the strength of the association was weaker in Japan. Similarly, Yoo et al. (2017) found that positive affect predicted healthy lipid profiles in the United States, but not in Japan. Clobert et al. (2019) suggest that cultural moderation of the association between positive affect and health might be particularly strong for high-arousal positive affect. Their findings, in fact, showed that high-arousal positive affect predicted self-reported health more strongly in the United States than in Japan, while low-arousal positive affect even showed a reversed pattern (Clobert et al., 2019).

Another aspect of psychological well-being, self-acceptance, includes awareness of not only personal strengths but also weaknesses, which may parallel ideas of self-criticism emphasized in Japanese Confucianism as routes to self-improvement (Heine et al., 2000). Similarly, self-compassion, which may encompass self-acceptance, is central to Buddhist world-views that are deeply rooted in Japanese culture (Dryden and Still, 2006). Self-compassion has been positively linked to supportive friendships and life satisfaction, and negatively to depression among Japanese respondents (Arimitsu, 2014; Yamaguchi et al., 2014; Taniguchi, 2015), while self-acceptance has been negatively linked with depression (Neff et al., 2008). Implications of any of these associations for physical health has not been previously considered.

Environmental mastery, another aspect of psychological well-being studied in the West, may be part of Japanese well-being, although for somewhat different reasons. Being in charge of one's situation may be valued in Japan not so much in terms of having individual power to influence outcomes, but because of the aim of minimizing difficulties for others (Kim et al., 2006). Thus, this dimension of well-being might be valued in both contexts, albeit for distinct life objectives.

Guided by the above ideas, the purpose of this study was to investigate links between longitudinal profiles of differing aspects of psychological well-being among Japanese adults with distinct aspects of health, also studied across time. Drawing on previous findings with a United States sample (Ryff et al., 2015), we focused on the contrast between those who showed persistently high vs. persistently low well-being across time. The rationale was that the majority of respondents (both in the United States and in Japan) showed stability in their well-being across time, albeit at different levels – some thus had cumulatively high profiles of well-being across time while others had cumulatively low profiles of well-being across time.

The indicators of well-being encompassed six dimensions of eudaimonic well-being (i.e., purpose in life, personal growth, positive relations with others[2], autonomy, self-acceptance,

[1]In Western cultures, positive relations with others has been consistently conceptualized as a central part of well-being (Ryff, 1989; Diener and Seligman, 2002), and have been linked to better health (Cohen, 2004), underscoring that individualism of Western cultures is not at the expense of social relations. Positive social relations fulfill universal human need to affiliate (Deci and Ryan, 2000) although cultural differences may exist in the specific nature of social relations.

[2]Although a certain aspect of social relations (i.e., maintaining social harmony) may have a greater importance in interdependent cultures than in independent cultures, the current study employed the conceptualization and measurement of social well-being established in Western cultures. Thus, we did not expect positive social relations to show a stronger association with health comparing to purpose in life or personal growth.

environmental mastery), and two dimensions of hedonic wellbeing (i.e., high-arousal positive affect, and general/low-arousal positive affect). Four separate measures of self-reported physical health were included: subjective health, chronic conditions, physical health symptoms, and functional health. The objective was to examine whether distinct dimensions of well-being mattered for all, or only some, aspects of cross-time health, thereby offering a comprehensive understanding of how persistently high versus persistently low well-being matters for unfolding profiles of physical health in Japanese adults.

Two overarching predictions guided the inquiry. First, we expected that persistently high levels of psychological well-being in certain domains (i.e., purpose in life, personal growth, positive relations with others) would be associated with health improvement across time in Japan. This prediction draws from prior literature suggesting cultural similarities in these areas of well-being, along with earlier evidence on their associations with health in Japan. Second, we hypothesized that persistently high autonomy and high-arousal positive affect would show weaker links to cross-time health, thus reflecting their reduced salience in the Japanese cultural context. Finally, two other aspects of well-being (self-acceptance, environmental mastery) did not include specific predictions, given the lack of theoretical or empirical guidelines from prior work.

MATERIALS AND METHODS

Participants

Participants were from a large longitudinal survey Midlife in Japan (MIDJA), conducted in 2008 and 2012. The first wave (MIDJA 1; 2008–2009) sampled 1,027 randomly selected adults residing in Tokyo metropolitan areas, aged 30–80. The second wave (MIDJA 2) was conducted in 2012–2013. Of the original 1,027 participants, 657 participants (70%) completed the longitudinal follow-up and are included in the following analyses. Details of the study protocol and data files are available on https://doi.org/10.3886/ICPSR30822.v3.

Measures

Eudaimonic well-being (Ryff, 1989) included six scales: autonomy, environmental mastery, personal growth, positive relations with others, purpose in life, and self-acceptance. Each scale consisted of seven items rated according to participants' degree of agreement with each item on a 7-point scale, ranging from 1 (strongly disagree) to 7 (strongly agree). Negative items were reverse-coded such that higher scores indicate higher levels of well-being. The internal consistencies (α) ranged from 0.68 to 0.79.

Hedonic well-being was measured by two types of positive affect. General/low-arousal positive affect was measured by Mroczek and Kolarz's (1998) scale. Participants were asked to report how frequently they felt each emotion during the past 30 days using of a 5 point-scale (1 = none of the time, 2 = a little of the time, 3 = some of the time, 4 = most of the time, and 5 = all the time). The items of emotions were cheerful, in good spirits, extremely happy, calm, and peaceful, satisfied, full of life. Second, high-arousal positive affect was measured by selective items form PANAS scale (Watson et al., 1988): enthusiastic, proud, active, and attentive. Participants reported the frequency of each item within the past 30 days on the 5-point scale. Alphas ranged from 0.79 to 0.93.

We used four measures of physical health: (1) subjective health, measured by one item asking participants to rate their current health on a scale, ranging from 0 (worst) to 10 (best); (2) number of chronic conditions experienced in the past 12 months (e.g., hypertension, stomach problems, arthritis). The score was constructed by taking the total number of "Yes" responses (ranging from 0 to 30). (3) Frequency of health symptoms measured by aggregating the frequency of nine different symptoms (e.g., headaches, joint stiffness) for the past 30 days (0 = not at all; 1 = once a month, 2 = several times a month, 3 = once a week, 4 = several times a week, and 5 = almost every day; ranging from 0 to 45) The alphas were 0.7 (Time 1) and 0.72 (Time 2). (4) Instrumental activities of daily living scale (IADL) measured functional health. Participants rated the extent to which their health limited various activities of daily living, ranging from basic activities (e.g., lifting or carrying groceries) to vigorous activities (e.g., running) on a 4-point scale (1 = not at all; 2 = a little; 3 = some; 4 = a lot). Thus, higher scores indicated more functional limitations. The alphas were 0.89 for both time points.

Demographic variables included age, gender (0 = male, 1 = female), and level of education (ranging from 1 = no school/some grade school to 8 = Ph.D., M.D., or other professional degree) were included. **Table 1** displays descriptive statistics and cross-time correlations for all variables. Measures of psychological well-being were highly correlated over 4–5 years (the average cross-time correlation = 0.67). The health measures showed lower cross-time correlations than well-being variables, with the exception of health symptoms.

TABLE 1 | Descriptive statistics of key variables at Time 1 and Time 2 (on cases for which longitudinal data were available).

	Mean (SD)		Cross-time *r*
	Time1	Time2	
Age	54.92 (13.58)	59.25 (13.54)	0.99
Education	4.54 (2.06)	4.55 (2.06)	0.96
% Male	47%	47%	
Autonomy	30.68 (5.5)	30.77 (5.14)	0.73
Environmental mastery	32.02 (5.53)	31.87 (5.19)	0.64
Personal growth	34.03 (5.69)	33.37 (5.67)	0.69
Positive relations	33.71 (5.82)	33.54 (5.57)	0.68
Purpose in life	31.82 (5.16)	31.4 (4.85)	0.64
Self-acceptance	31.13 (5.8)	30.9 (5.39)	0.73
General/low-arousal PA	3.28 (0.77)	3.26 (0.65)	0.64
High-arousal PA	3.09 (0.74)	3.06 (0.77)	0.57
Subjective health	6.36 (1.93)	6.23 (2.05)	0.51
Chronic conditions	2.28 (2.01)	2.13 (1.88)	0.57
Health symptoms	12.02 (7.51)	13.49 (7.91)	0.68
Function health (IADL)	1.39 (0.65)	1.51 (0.76)	0.42

Longitudinal Profiles of Well-Being

Consistent with findings from the United States (Ryff et al., 2015), most MIDJA participants showed stable levels of well-being across the 4–5-year period. That is, only 16% or less of the sample reliably changed (Jacobson and Truax, 1991) on any dimension of well-being between the two waves. However, participants were stable at different levels of well-being. To classify individuals' cumulative well-being over the 4–5 years, respondents were categorized into five groups: persistently low (stable low), persistently moderate (stable mid), persistently high (stable high), increasing and decreasing (see **Figure 1**). Quartiles cuts at each wave were used to define these groups. Similar to the reliable change index (Jacobson and Truax, 1991), change was defined as moving upward (increasing) or downward (decreasing) 2+ quartiles from Time 1 to Time 2. All other groups were defined as stable, albeit at different levels (low, moderate, high). **Table 2** presents the percentages of categories for each well-being dimension. Most Japanese respondents (84–91%) showed high stability over time across all dimensions of well-being. These were apportioned into three varieties of stability: persistently low (24–31%), persistently moderate (29–38%), and persistently high (23–30%). The rest (9–16%) met criteria for increasing or decreasing on the various aspects of well-being.

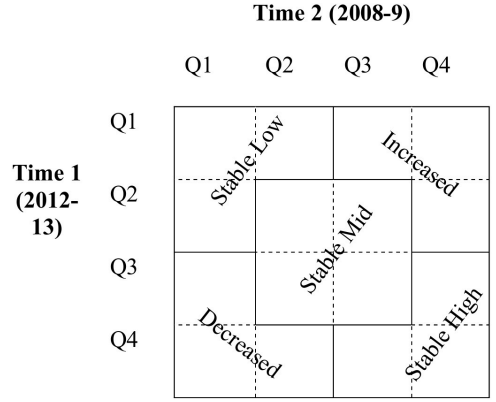

FIGURE 1 | Categorization of longitudinal profiles of well-being based on the quartiles of Time 1 and Time 2 well-being levels.

TABLE 2 | Categories of longitudinal profiles of well-being.

	Stable low (%)	Stable mid (%)	Stable high (%)	Increase (%)	Decrease (%)
Eudaimonic well-being					
Autonomy	28.5	34.1	26.6	5.1	5.7
Environmental mastery	27.3	30.7	26.9	8.4	6.7
Personal growth	26.6	35.4	28	6.2	3.7
Positive relations	24.2	34	29.8	6.5	5.4
Purpose in life	30	28.6	25.9	9	6.5
Self-acceptance	23.9	38.2	28.4	5.6	3.9
Hedonic well-being					
General	25.9	32.8	29.1	6.5	5.7
High-arousal	31.5	30.7	23.1	8.2	6.5

RESULTS

The core aim was to test whether persistently high versus low levels of psychological well-being would predict better physical health over 4–5 years. We conducted hierarchical linear regression analyses in which each measure of well-being predicted each measure of health outcome in a separate model. In the first step of the model, demographic variables and Time 1 baseline health were entered to predict Time 2 health. By including Time 1 health, the coefficients represent the associations between predictors and residualized changes in health from Time 1 to Time 2. In the next step, dummy-coded well-being was entered, in which stable high was used as a reference group compared to four other groups (i.e., stable low, stable mid, decreasing, increasing).

The summary of results is displayed in **Table 3**. Contrasts between stable high and increasing or decreasing groups are not presented because they had few observations, thereby yielding less reliable estimates for the contrasts. Although primary interest was in the contrast between stable high and stable low, the contrast between stable high and stable mid informs the strength of the effect linking different levels of stability in well-being to cross-time changes in health.

Subjective Health

For all six scales of eudaimonic well-being, respondents with stable low profiles had worse subjective health at Time 2 compared to those with stable high profiles. For environmental mastery, personal growth, and positive relations with others, those with stable mid well-being also had worse health compared to those with stable high well-being. Autonomy explained smaller variances, $R^2\Delta = 0.008$, compared to other dimensions of eudaimonic well-being, $R^2\Delta = 0.018$–0.042.

For both measures of hedonic well-being, those with stable low profiles showed worse health than those with stable high profiles. In addition, for general/low-arousal positive affect, those with stable mid profiles had worse health than those with stable high profiles. The effect size of general/low-arousal positive affect was slightly larger, $R^2\Delta = 0.032$, than high-arousal positive affect, $R^2\Delta = 0.028$.

Chronic Conditions

For all scales of eudaimonic well-being except for positive relations with others, those with stable low well-being reported more chronic conditions in 5 years compared to those with stable high well-being. Unlike subjective health, the effect size of autonomy was, $R^2\Delta = 0.017$, comparable with other dimensions (e.g., self-acceptance: $R^2\Delta = 0.014$).

For both measures of hedonic well-being, those with stable low profiles reported greater increments in chronic conditions than those with stable high profiles. General/low-arousal positive affect explained more variance of the chronic conditions, $R^2\Delta = 0.023$, compared to high-arousal positive affect, $R^2\Delta = 0.010$.

TABLE 3 | The effect sizes ($R^2\Delta$) and unstandardized coefficients (b) of models in which longitudinal well-being predict health outcomes.

Health measures		Subjective health		Chronic conditions		Health symptoms		Functional health	
		Stable high vs. stable low	Stable high vs. stable mid	Stable high vs. stable low	Stable high vs. stable mid	Stable high vs. stable low	Stable high vs. stable mid	Stable high vs. stable low	Stable high vs. stable mid
Eudaimonic well-being									
Autonomy	*b*	−0.431*	−0.228	0.589***	0.196	1.684*	1.251*	2.35**	2.258**
	$R^2\Delta$	0.008		0.017		0.012		0.012	
Environmental mastery	*b*	−0.855***	−0.377*	0.875***	0.184	2.609***	1.111$^+$	2.904**	2.512**
	$R^2\Delta$	0.034		0.033		0.017		0.015	
Personal growth	*b*	−0.806***	−0.349*	0.516**	0.266$^+$	1.22$^+$	1.003	2.493**	1.103
	$R^2\Delta$	0.031		0.010		0.01		0.009	
Positive relations	*b*	−0.950***	−0.476**	0.314$^+$	0.056	1.705*	1.754**	2.552**	0.029
	$R^2\Delta$	0.037		0.008		0.015		0.013	
Purpose in life	*b*	−0.617**	−0.280	0.492**	0.038	1.82**	1.081	2.883**	1.366
	$R^2\Delta$	0.018		0.018		0.007		0.014	
Self-acceptance	*b*	−0.797***	−0.759***	0.586**	0.083	1.689*	0.038	2.904**	1.963*
	$R^2\Delta$	0.042		0.014		0.008		0.013	
Hedonic well-being									
General/low-arousal	*b*	−0.906***	−0.460**	0.702***	0.300$^+$	0.945	0.712	1.237	0.704
	$R^2\Delta$	0.032		0.023		0.011		0.003	
High-arousal	*b*	−0.745***	−0.234	0.492**	0.160	1.314$^+$	0.759	2.317**	1.774*
	$R^2\Delta$	0.028		0.010		0.007		0.010	

*Models included age, gender, education, and Time 1 health as covariates. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, $^+p < 0.1$.*

Health Symptoms

The increase in health symptoms was greater for those with stable low well-being than those with stable high well-being, across all dimensions of eudaimonic well-being except personal growth. In additions, those with stable mid-levels of positive relations with others and autonomy had more health symptoms compared to those with the stable high-levels. Consistent with the results for chronic conditions, the effect size of autonomy was comparable to other dimensions of eudaimonic well-being. For hedonic well-being, neither general/low-arousal nor high-arousal positive affect predicted changes in health symptoms.

Functional Health

Those with stable low well-being reported more physical limitations in daily activities than those with stable high well-being across all dimensions of eudaimonic well-being. For environmental mastery, autonomy, and self-acceptance, those with stable mid well-being had worse functional health compared to those with stable high well-being. Again, the effect size of autonomy was comparable to other dimensions of eudaimonic well-being.

The association between hedonic well-being and functional health for daily activities showed a different pattern from other health outcomes. Cumulative profiles of high-arousal positive affect predicted greater increments in functional health whereas the profiles of general/low-arousal positive affect did not predict functional health. Those with stable high high-arousal positive affect reported relative improvement in functional health compared to those with stable low and stable mid high-arousal positive affect.

DISCUSSION

The study yielded consistent patterns of results across dynamic measures of health that were predicted by cumulative profiles of diverse aspects of psychological well-being in Japanese adults. Specifically, persistently high levels of psychological well-being predicted improved subjective health, fewer chronic conditions, fewer health symptoms, and fewer functional health problems over 4–5 years compared to persistently low levels of psychological well-being. Persistently high levels of psychological well-being also predicted better subjective health, fewer health symptoms, and fewer functional limitations compared to persistently moderate levels of psychological well-being, suggesting that health improvement associated with higher psychological well-being may not be limited to those with extreme levels of psychological well-being. Together, the findings extend a prior literature focused on longitudinal associations between psychological well-being and health in United States adults to another cultural context, namely, Japan.

For all six dimensions of eudaimonic well-being, Japanese adults with persistently high profiles of well-being showed greater health improvement (i.e., higher subjective healthy, reduced chronic conditions and health symptoms, fewer functional limitations) than those with stable low profiles of well-being. This was true even for autonomy, which is less culturally valued in in Japan compared to the United States It is notable that such effects were evident despite a notably shorter follow-up period in Japan (4–5 years) compared to the longer period (9–10 years) found for United States adults (Ryff et al., 2015). Overall, the patterns convey that cumulatively high levels of eudaimonic well-being

point to similarly benefits for cross-time health in both Japan and the United States.

For hedonic well-being, persistently high levels of both low- and high-arousal positive affect predicted improved subjective health and fewer chronic conditions than persistently low levels of hedonic well-being. The results partially supported our hypotheses that high-arousal positive affect would show weaker association with health than general/low-arousal positive affect in Japan, except for functional health. These are consistent with prior research showing that low-arousal positive affect was more strongly associated with health than high-arousal positive affect in Japan (Clobert et al., 2019). Cumulative profiles of hedonic well-being did not predict change in health symptoms, contrary to eudaimonic well-being. Given that health symptoms were the most stable measure of health over 4–5 years (cross-time $r = 0.68$), it can be speculated that the effect of hedonic well-being on change in health may be more contingent on the stability of health measures than eudaimonic well-being.

Lastly, change in functional health was associated with only high-arousal positive affect. The different results for functional health could be attributed to that its measure included engagement in high-arousal activities (i.e., running). To investigate this possibility, we ran three separate models testing whether high-arousal positive affect measured at Time 1, Time 2, or the change between the two time points would predict Time 2 functional health (controlling for Time 1 functional health). The only significant predictor was Time 2 high-arousal positive affect, indicating that the findings are accounted by the concurrent association between high-arousal positive affect and functional health, rather than the effect of high-arousal positive affect on health over time.

Overall, psychological well-being accounted for small variances in Time 2 health. These small effect sizes were expected because the models predicted Time 2 health adjusted for Time 1 health; the residual changes in health were small between the relatively short interval (i.e., 4–5 years). Nonetheless, the small effect sizes were comparable to prior studies with Western samples that examined the associations between psychological well-being and prospective health outcomes such as mortality and longevity (Chida and Steptoe, 2008; Xu and Roberts, 2010), suggesting that even small effects can have practical implications.

The key limitation of the study is that the analyses cannot rule out the reversed causality between well-being and health. Cumulative profiles of well-being were created based on Time 2 as well as baseline measure, which do not temporally precede Time 2 health. Thus, the associations between health and persistent levels of well-being could be partly due to the effect of health improvement on well-being. With the exception of the result for functional health and high arousal positive affect, however, the variance of Time 2 health (net of Time 1 health) explained by cross-time well-being was greater than the variance of Time 2 well-being (net of Time 1 well-being) explained by cross-time health. This suggests that the observed associations were likely derived by the influence of cross-time well-being on health, though the alternative explanation cannot be rejected.

In addition, the findings are based on single-sourced, self-reported measures of health. Although prior studies have shown that self-reported health including subjective health and chronic conditions are valid indicators of physical health (e.g., Bound, 1989; Idler and Benyamini, 1997; Miilunpalo et al., 1997), future research should examine whether the effects can be expanded to objective measures of health from multiple sources (e.g., Radler et al., 2018). Moreover, the current study used longitudinal data only measured at two time points, which did not allow other statistical methods that classify longitudinal profiles of continuous variables with more precision (e.g., latent transition analysis). Nonetheless, the current approach of focusing on cumulative profiles of well-being aimed to provide a starting point to investigate effects of stable levels of well-being on dynamic aspects of health.

Although comprehensive measures of well-being were employed, all were developed based on the theories formulated in the Western cultures. It is possible that these measures miss certain aspects of well-being specific to Japanese cultures. For instance, the study did not have an adequate measure of harmonious social relationships that receives a great emphasis in Japanese cultures. Although positive relations with others was included as an aspect of well-being, this measure focuses on perceptions of warm and trusting relationships (Ryff, 1989) whereas harmonious social relationships in Japan are often evaluated at a group level, including external viewpoints (e.g., fulfilling expectations of close others). Including more culturally relevant measures of well-being might reveal even stronger effect sizes in associations between well-being with health in Japan.

Despite the limitations, the study is unique in that it examined multiple dimensions of psychological well-being to test longitudinal relationships between cumulative well-being and change in health in a different culture. The use of multi-dimensional approach is particularly important in considering cultural contexts, given that some dimensions have more cultural variation than others. Furthermore, by focusing on the stable levels of well-being, the study was able to examine health implications of well-being for which most people do not show reliable changes. The findings showed health predictability of persistent level of psychological well-being even when controlling for baseline health in Japan, highlighting the importance of cumulative psychological well-being in health benefits in diverse cultural contexts.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Wisconsin–Madison Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JY carried out the data analysis and drafted the manuscript under the supervision of CR. Both authors developed the study concept and approved the final version of the manuscript for submission.

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SYSTEMATIC REVIEW
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A Systematic Review of Metacognitive Beliefs in Chronic Medical Conditions

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Background: Psychological functioning plays an important role in medical conditions and impacts patients' quality of life. Previously, many studies have highlighted the association of metacognition to both the development and maintenance of emotional disorders. Recently, several researchers pointed out the relevant role of dysfunctional metacognitive beliefs in the context of chronic diseases. Hence, dysfunctional metacognitive beliefs could be directly related to anxiety and depression, regardless of the medical condition's expression. The aim of this systematic review was to summarize the available evidence regarding the association of metacognition with anxiety, depression, and perceived quality of life, in the context of medical conditions, according to Wells' theory.

Methods: A systematic review based on electronic bibliographic databases (PsycINFO, PubMed, Scopus, Web of Science, and Web of Knowledge) of scientific literature was carried out. Studies involving patients evaluated in clinical settings were included in the analysis.

Results: Our findings indicated that metacognition appears to be related to anxiety, depression, and quality of life in patients with medical chronic conditions. Therefore, dysfunctional metacognitive beliefs might be a relevant factor associated with the process of adapting to illness.

Conclusions: The additional evaluation of metacognitive factors in the context of several medical chronic conditions appears valuable. Due to the rising interest in the study of metacognition, suggestions for future research have also been provided.

Keywords: metacognition, MCQ-30, cognitive attentional syndrome (CAS), metacognitive beliefs, chronic medical conditions, anxiety, depression

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INTRODUCTION

Rationale

In the past few decades, the role of metacognition in psychopathology has received increased attention. The term metacognition refers to "the aspect of information processing that monitors, interprets, evaluates, and regulates the contents and processes of its organization" (Wells and Purdon, 1999, p. 103). A growing body of research has highlighted that metacognition is associated with the development and the maintenance of psychological disorders. An important

approach in this regard is exemplified by the Self-Regulatory Executive Function (S-REF) model, proposed by Wells and Matthews (1996). The principal feature of this model is that it points out the transdiagnostic process involved in emotional disorders. The main focus is not on the symptoms or the diagnosis, but is instead on the dysfunctional metacognitive beliefs and the emotional self-regulation strategies behind them. In fact, the vulnerability and the prolongation of disorders are associated with a non-specific style of thinking, named cognitive attentional syndrome (CAS) (Wells, 2000a,b). CAS refers to repetitive negative thinking in the process of worrying and ruminating, driven by the positive and negative beliefs about worry, concerns about uncontrollability and danger, and the limitations on executive control. The strategies of pathological worry, rumination, and threat monitor describe positive beliefs, while the beliefs about the danger and the uncontrollability of certain thoughts characterize negative beliefs. Some examples of positive beliefs are: "Worrying helps me cope," or, "Worrying helps me solve problems." Examples of negative beliefs are: "My worrying is dangerous for me," and "My worrying could make me go mad." Consistent with this metacognitive theory of emotional disorders, a series of self-report instruments for assessing dysfunctional metacognitive beliefs were developed. The Metacognitions Questionnaire (MCQ) and its short version (MCQ-30) measure a range of metacognitive beliefs and processes which are considered relevant to the psychological vulnerability and maintenance of emotional disorders (Cartwright-Hatton and Wells, 1997; Wells and Cartwright-Hatton, 2004; Quattropani et al., 2015).

Earlier studies involving clinical samples have shown that metacognitive beliefs are linked to a wide range of psychopathological conditions, such as anxiety disorder (Wells and Carter, 2001), obsessive-compulsive symptoms (Wells and Papageorgiou, 1998), schizophrenic disorders (Larøi et al., 2004; García-Montes et al., 2006), and anorexia nervosa (Cooper et al., 2007).

Recently, a growing number of studies has investigated the role of metacognition even in non-clinical samples. Main findings pointed out that metacognitive beliefs were significantly associated with either perceived stress or negative emotions (Spada et al., 2008b). In addition, dysfunctional metacognitive beliefs predicted the onset of anxiety and depression symptoms in the context of stressful life events (Yilmaz et al., 2011). Moreover, the negative beliefs factor was the strongest predictor for both anxiety and depression (Spada et al., 2008a).

Researchers are becoming increasingly interested in this field as dysfunctional metacognitive beliefs appear to be common factors across a wide range of psychopathologies (Sun et al., 2017).

Currently there are several studies that have demonstrated that metacognitions are involved in the perpetuation of psychological disorders. Therefore, in recent years, systematic reviews and meta-analyses have been carried out on the basis of the available data. Preliminary results suggested that interventions based on metacognition may be effective in anxiety and depressive disorders treatment (Knowles et al., 2016; Normann and Morina, 2018). The greater prevalence of dysfunctional metacognitive beliefs has recently been associated with clinical psychosis (Sellers et al., 2016, 2018).

In recent years, the role of metacognition was investigated in patients with chronic conditions and their caregivers. Anxiety and depression symptoms are common in a wide range of chronic medical conditions, influencing the patients' quality of life (Marchetti et al., 2017; Catalano et al., 2018; Marchini et al., 2018; Martino et al., 2018, 2019c,d,e; Quattropani et al., 2018a,b; Fantinelli et al., 2019; Lenzo et al., 2019). Dysfunctional metacognitive beliefs could be a relevant factor involved in the development of negative emotions, influencing the adherence to medical treatments. In the light of this perspective, metacognitive beliefs of chronic patients and their caregivers could be a significant factor related to the development of distress. Some researchers have started examining this topic. For example, when patients with multiple sclerosis tend to adopt a dysfunctional metacognitive strategy, metacognition can become a relevant therapeutic tool (Pöttgen et al., 2015). The results of a recent study showed insignificant differences between metacognitive factors of multiple sclerosis patients and healthy subjects. Both conflicting and specific correlations between multiple sclerosis patients and control subjects were found (Quattropani et al., 2018c). In addition, coherent findings were revealed in the first research involving cancer patients (Quattropani et al., 2016). Conditions such as cancer are often characterized by the difficulty in the process of making sense integration of the traumatic event and coping, during the first phase (Martino et al., 2019a,b). The process of "making sense," as a subjective experience, is an important element in promoting a patient's well-being after a traumatic event such as cancer and its related treatments (Martino and Freda, 2016; De Luca Picione et al., 2017). According to this perspective, metacognitions can play a crucial role in the adaptation process of patients and their quality of life. More generally, a deep understanding of the psychological functioning of patients with chronic medical conditions could be useful in implementing tailored psychological interventions in medical settings (Dicé et al., 2016, 2018, 2019).

Despite the considerable amount of studies conducted in the context of chronic medical conditions, there is still a lack of a rigorous and careful summarization of the evidence.

Objectives

This systematic review aimed at ascertaining the relevance of dysfunctional metacognitive beliefs among patients with chronic medical conditions and/or their caregivers through the analysis of the studies employing the MCQ and the MCQ-30.

Research Question

We hypothesized that metacognitive beliefs might interact with the experience of a chronic medical condition and contribute to it worsening, affecting psychological distress in both patients and their caregivers.

METHODS

The authors followed the Preferred Reporting Items for Systematic Reviews and Meta Analyses—PRISMA (Liberati et al.,

2009; Moher et al., 2009) guidelines for the drafting of this systematic review.

Search Strategy and Data Sources

A systematic review of the literature was conducted in two stages. Initially, the studies were identified by searching PubMed, WebOfKnowledge, and Scopus using the following keywords: "metacognition," "metacognitive beliefs," "metacognition* questionnaire," "meta-cognition* questionnaire." We preliminarily filtered the online search by language (English) and species (Humans). The online search was completed on 30th April 2019.

Eventually, the reference lists of the included studies were examined to identify possible relevant studies missed during the database search.

Inclusion and Exclusion Criteria

Original papers written in English with an available full text were included in the review. Included articles contained information about the subjects affected by chronic medical conditions and/or the patients' caregivers. Studies which employed the "Metacognitive Questionnaire" (MCQ-65) or its brief variant (MCQ-30) as metacognition measure were also included. This review aimed at generically evaluating metacognition, rather than selectively investigating the specifically related symptoms such as paranoia or delusions. In line with this premise, any other tool aimed at assessing metacognition was excluded.

We also excluded articles primarily involving patients with psychiatric conditions, according to the DSM-5 or ICD-10 (World Health Organization, 1992; American Psychiatric Association, 2013), as well as the studies involving only healthy subjects.

The ones which did not clearly provide data on the subjects' medical conditions or the assessment of metacognition were excluded.

Eligibility Screening

The eligibility was assessed in a three-step procedure by two different authors (VL, AS): first by the title, then by the abstract, and finally by a full text screening. Conflicts regarding eligibility were resolved by consulting a senior author (MQ).

The review articles were not assessed for eligibility, however they were used as a source for potential further studies not previously identified.

Data Extraction

Data were extracted following a preliminary coding protocol shared by all the authors. The extraction of the studies' characteristics included the clinical sample type and demographic features, the study design, the measures of metacognitive beliefs, and if evaluated, the pre- and post-observations of the metacognitive therapy efficacy.

The extraction of the study data also included the aims, hypotheses, and key findings (including the correlation coefficients or the means and standard deviations).

Quality Assessment

The Newcastle Ottawa Scale (NOS) for quality assessment was employed in this systematic review (www.ohri.ca/programs/clinical_epidemiology/oxford.asp).

Since the majority of the included studies were designed as cross-sectional, we additionally employed an adapted version of the NOS for cross-sectional studies, as previously used (Herzog et al., 2013). The validated NOS for quality assessment was employed for the remaining included studies designed as case-controlled.

Two independent authors (VL, AS) assessed the methodological quality of the retrieved evidence in order to identify any potential source of bias. Disagreements were resolved by consensus with a senior author.

A summary of the quality assessment of included studies is provided in **Tables 2**, **3**.

RESULTS

Literature Search Results

An overview of the screening procedure is provided in **Figure 1**. The online search strategy retrieved 5,573 papers; a secondary independent manual search retrieved a further seven articles. After removing 1,466 duplicates, 4,114 articles were screened by the title/abstract. A total of 412 full text articles were consequently assessed for eligibility. Finally, 31 studies were included in the systematic review.

Included Studies

A summary of the included studies' characteristics is provided in **Table 1**.

The majority of included studies were designed as cross-sectional. A limited number of studies involved a control group.

The majority of the studies involved patients with cancer or different neurological diseases. Studies on Chronic Fatigue Syndrome, Diabetes, Sexual Dysfunctions, Chronic Pain, and HIV were also retrieved and included in the systematic review.

Metacognition and Cancer

The potential role of metacognitive beliefs in subjects with cancer has been a debated research topic in the last few years. The MCQ-30 has been recently validated in a primary breast/prostate cancer population and it is actually considered a valid measure of metacognition among these patients (Cook et al., 2014a); subjects with cancer were found to exhibit more negative metacognitive beliefs compared to healthy subjects (Mutlu et al., 2018).

Metacognitive beliefs are also associated with the symptoms of anxiety, depression, and post-traumatic stress disorder (PTSD), and they independently explain the additional variance in these outcomes even after controlling for demographic characteristics and illness perceptions (Cook et al., 2014b, 2015). Moreover, it was recently discussed that negative beliefs highly correlated to anxiety and depression, and were also independently associated with anxiety in subjects undergoing chemotherapy (Quattropani et al., 2016, 2017a).

Patients experiencing the fear of cancer recurrence (FCR), often show dysfunctional metacognitive beliefs,

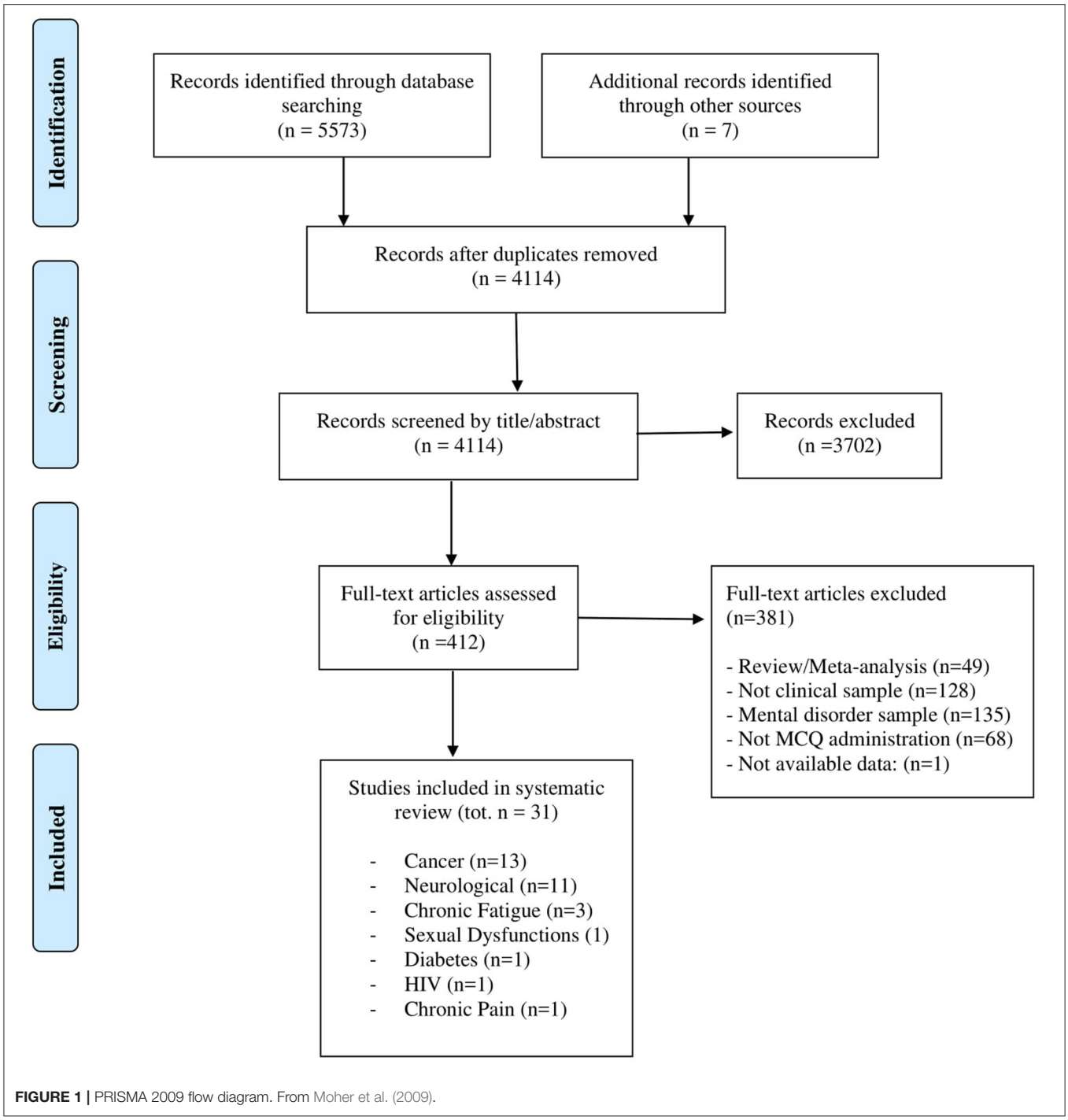

FIGURE 1 | PRISMA 2009 flow diagram. From Moher et al. (2009).

particularly positive beliefs about worry and beliefs about the uncontrollability and dangers of worrying (Butow et al., 2015). In a recent randomized controlled trial (RCT), the efficacy of a multidimensional intervention, based on metacognition training, in reducing the fear of cancer recurrence was demonstrated. At the end of the trial, subjects also exhibited lower maladaptive metacognitive beliefs (Butow et al., 2017).

The potential positive role of metacognition therapy (MCT) has also been investigated in young cancer survivors who commonly show signs of dysfunctional metacognitive beliefs associated with emotional distress and post-traumatic stress symptoms (PTSS) (Fisher et al., 2018a): MCT was shown to be effective in reducing anxiety and depression symptoms (Fisher et al., 2015).

The MCT sessions appear as having a positive effect even on reducing the levels of anxiety, depression, FCR, post-traumatic stress symptoms, health-related quality of life, worry/rumination,

TABLE 1 | Characteristics of the included studies.

Study	Clinical sample	Study design	MC tool	Main findings
Allott et al. (2005)	Parkinson's disease ($n = 44$)	Cross-sectional	MCQ-30	Dysfunctional metacognitive style is independently associated with the increased vulnerability to distress ($p < 0.05$).
Bagcioglu et al. (2012)	Premature ejaculation ($n = 40$) Erectile dysfunction ($n = 40$) Healthy controls ($n = 80$)	Case-controlled Cross-sectional	MCQ-30	The total MCQ-30 score was significantly higher in the patients with premature ejaculation and an erectile dysfunction ($p < 0.05$). The positive beliefs, negative beliefs scores were significantly higher in patients with sexual disorders ($p < 0.05$).The cognitive self-consciousness score was significantly higher in the patients with premature ejaculation, than the erectile dysfunction group ($p < 0.05$), and the healthy controls ($p < 0.05$).
Brown and Fernie (2015)	Parkinson's disease ($n = 106$)	Cross-sectional	MCQ-30	Metacognitive factors were significantly correlated to anxiety when controlling for the motor experiences of daily living and the intolerance of uncertainty, $R^2 = 0.56$, $F_{(1,82)} = 15.04$, $p < 0.001$ (adjusted $R^2 = 0.53$). Metacognitions regarding uncontrollability and danger were significantly correlated to off-period distress when controlling for the motor experiences of daily living, the intolerance of uncertainty, and other metacognitive factors, $\chi 2(1) = 20.52$, $p = 0.001$.
Butow et al. (2015)	Breast/prostate cancer ($n = 63$)	Cross-sectional	MCQ-30	Survivors with the clinical fear of cancer recurrence (FCR) had significantly higher positive beliefs about worry (10.1 vs. 7.4, $p = 0.002$) and beliefs about the uncontrollability and dangers of worrying (12.0 vs. 7.7, $p = 0.000$), than those with non-clinical FCR. Total metacognition scores were significantly correlated to FCR in the multiple regression analysis ($\beta = 0.371$, $p = 0.001$).
Butow et al. (2017)	Breast/colorectal cancer or Melanoma (Intervention group $n = 121$; Control group $n = 101$)	Randomized controlled trial	MCQ-30 (+MCT)	The efficacy of intervention based on attention training, metacognition, acceptance, screening behavior, and values-based goal setting, compared to the intervention based only on attention control, resulted in the reduction of Fear of Cancer Recurrence Inventory (FCRI) immediately post-therapy, and 3 and 6 months later. The participants also showed a significantly higher T0 to T1 improvement in total MCQ30 ($P = 0.042$) and the need to control thoughts ($P = 0.004$), than controls.
Cook et al. (2014a)	Breast/prostate cancer ($n = 229$)	Cross-sectional (validation of MCQ-30 for cancer)	MCQ-30	Confirmatory and exploratory factor analyses supported the validity of the 5-factor structure of the MCQ-30. The structural equation modeling indicated that the two dimensions of metacognition (positive and negative beliefs about worry) were significantly associated to anxiety and depression.
Cook et al. (2014b)	Breast/prostate cancer ($n = 206$)	Prospective cohort study	MCQ-30	Metacognitive beliefs ("negative beliefs about worry," "positive beliefs about worry," "cognitive confidence") explained 19% of the variance in anxiety, 15 % of the variance in depression and 14 % of the variance in trauma after 12 months post the cancer diagnosis.
Cook et al. (2015)	Breast/prostate cancer ($n = 229$)	Cross-sectional	MCQ-30	Regression analysis showed that metacognitive beliefs were associated to the symptoms of anxiety, depression, and PTSD.
Donnellan et al. (2016)	Post-stroke ($n = 64$)	Cross-sectional	MCQ-30	The total MCQ-30 scores were significantly associated to both, anxiety ($r = 47$, $P = 0.001$) and depression ($r = 0.54$, $P < 0.0001$). The MCQ-30 subscales "cognitive confidence," "cognitive self-consciousness," and "uncontrollability/danger" were the specific factors to be associated to the mood symptoms ($P < 0.01$). Metacognition remained a statistically significant factor associated to depression ($\beta = 0.42$, $P < 0.0001$) and anxiety ($\beta = 0.51$, $P < 0.0001$) after adjusting for education and global cognition.

(Continued)

TABLE 1 | Continued

Study	Clinical sample	Study design	MC tool	Main findings
Fernie et al. (2015)	Chronic Fatigue Syndrome ($n = 171$) (CBT group $n = 115$; GET group $n = 55$)	Cross-sectional Controlled	MCQ-30	The changes on the subscales of the MCQ-30 were found significantly associated to fatigue severity independently of the changes in depression and anxiety, and across the treatment modalities (CBT and GET).
Fisher et al. (2019)	Cancer survivors ($n = 27$)	Open trial (3- and 6 months follow-up)	MCQ-30 (+MCT)	MCT was associated to the statistically significant reductions across all psychological outcomes (anxiety, depression, fear of cancer recurrence, post-traumatic stress symptoms, health-related quality of life, and metacognitive beliefs) which were maintained throughout the 6-month follow-up.
Fisher et al. (2018a)	Cancer survivors ($n = 87$)	Cross-sectional survey	MCQ-30	The MCQ-30 subscales were all positively correlated to the emotional distress and post-traumatic stress symptoms, with the "Negative Beliefs about Worry" subscale strongly correlating to both the distress ($r = 0.74$, $p < 0.01$) and the post-traumatic stress ($r = 0.70$, $p < 0.01$).
Fisher et al. (2018b)	Epilepsy ($n = 457$)	Cross-sectional survey	MCQ-30	The hierarchical regression analyses demonstrated that metacognitive beliefs and illness perceptions were both associated to anxiety and depression when controlling for the influence of demographic variables and epilepsy characteristics. However, metacognitive beliefs accounted for more variance in anxiety and depression, than the illness perceptions.
(Fisher and Noble, 2017)	Epilepsy ($n = 349$)	Cross-sectional survey	MCQ-30	After controlling for demographics, epilepsy characteristics, comorbid physical and/or psychiatric illnesses, metacognitive beliefs explained an additional 20% of the variance in anxiety and 24% additional variance in depression. The relationship between the negative metacognitive beliefs about the uncontrollability and the dangers of worrying and the anxious and depressive symptoms was partially mediated by worry.
Fisher et al. (2017)	Cancer survivors ($n = 4$)	Non-concurrent multiple baseline design with 3- and 6-months follow-up	MCQ-30 (+MCT)	MCT was associated to clinically significant reductions in anxiety, depression, fear of cancer recurrence, worry/rumination, and metacognitive beliefs at the end of treatment, and the gains were maintained in all the patients to the 3 months follow-up and in three out of four patients, to the 6-months follow-up.
Fisher et al. (2016)	Epilepsy ($n = 349$)	Cross-sectional (validation of MCQ-30 for epilepsy)	MCQ-30	The MCQ-30 was found to be a robust measure of metacognitive beliefs and processes and has clinical utility for the subjects with epilepsy.
Fisher et al. (2015)	Adolescent/Young adult Cancer survivors ($n = 12$)	Pilot open trial (6 months follow-up)	MCQ-30 (+MCT)	MCT was associated to the large and statistically significant reductions in anxiety, depression, trauma symptoms, and metacognitive beliefs and processes. In the intention-to-treat sample, 50% of participants met the standardized criteria for recovery on the HADS post-treatment and these gains were maintained through to 6-month follow-up.
Gill et al. (2015)	Traumatic brain injury ($n = 47$) Subarachnoid hemorrhage ($n = 93$)	Cross-sectional	MCQ-30	All the metacognitive variables were positively correlated to PTSS severity: positive metacognitive beliefs about worry ($r = 0.35$, $p < 0.01$), negative metacognitive beliefs about worry ($r = 0.63$, $p < 0.01$) and beliefs about the need to control thoughts ($r = 0.54$, $p < 0.01$). The metacognitive factors were able to explain an additional and significant amount of variance in PTSS severity within the regression analysis.
Heffer-Rahn and Fisher (2018)	Multiple sclerosis ($n = 132$)	Cross-sectional	MCQ-30	Four of the metacognition subscales were positively associated with distress (PMCBS, NMCBS, CC, and NC, $r = 0.37$–0.49, $p < 0.01$). An hierarchical regression predicting distress showed that the metacognitive variables made a significant contribution to the variance in distress, accounting for an additional 4.5% of the variance ($F_{change} = 2.695$, df = 5,113, $p < 0.05$).

(Continued)

TABLE 1 | Continued

Study	Clinical sample	Study design	MC tool	Main findings
Jacobsen et al. (2016)	Chronic fatigue with subjective cognitive impairment ($n = 137$)	Cross-sectional (pre-post-occupational therapy observation)	MCQ-30	The total MCQ-30 score and the "cognitive confidence" subscale score were significantly associated to the subjective cognitive impairments at the baseline ($p < 0.0001$). The pre-treatment (occupational therapy) scores on "cognitive confidence" were significantly associated with the post-treatment scores on the EMQ ($p < 0.0001$). A hierarchical regression showed that a reduction on MCQ-30 total score was significantly associated to a reduced post-treatment score on the EMQ. Post-treatment scores on "cognitive confidence" were significantly associated with post-treatment scores on the EMQ.
La Foresta et al. (2015)	Amyotrophic Lateral Sclerosis (ALS) patients' caregivers with executive dysfunction ($n = 22$)	Cross-sectional	MCQ-30	The MCQ-30 total score is positively correlated to the number of perseverative errors on the Wisconsin Card Sorting Test (0.75 $p < 0.001$). In particular, the "need to control thoughts" is positively correlated to the number of perseverative errors (0.78 $p < 0.001$).
Maher-Edwards et al. (2011)	Chronic Fatigue Syndrome ($n = 96$)	Cross-sectional	MCQ-30	The correlation analysis showed that metacognitions were positively correlated to the measures of symptom severity, independently of anxiety, and depression. A hierarchical regression analysis indicated that the lack of cognitive confidence was associated to the mental and physical factors of the CFQ, and to the physical functioning independently of the negative emotions. The beliefs about the need to control thoughts was associated to the mental factor of the CFQ independently of the negative emotions and the lack of cognitive confidence.
Mutlu et al. (2018)	Cancer ($n = 279$) Controls ($n = 212$)	Cross-sectional Case controlled	MCQ-30	There was a significant effect in the group on the total MCQ-30 for the two conditions [$F_{(1,489)} = 56.57$, $p = 0.00$]. The patients scored significantly higher on all the subscales of the MCQ- 30, compared to the control group. The patients had consistently higher levels of negative metacognitions, compared to the control group regardless of the specific cancer diagnosis.
Purewal and Fisher (2018)	Type1 Diabetes ($n = 335$) Type2 Diabetes ($n = 279$)	Cross-sectional	MCQ-30	The regression analysis showed that metacognitive beliefs were associated to anxiety and depression in the patients with diabetes (PwD) and explained the additional variance in both, anxiety and depression after controlling for demographic variables and illness perceptions.
Quattropani et al. (2018d)	Amyotrophic lateral sclerosis caregivers ($n = 70$)	Cross-sectional	MCQ-30	Metacognition was significantly related to the state and the traits of anxiety, cognitive, and the somatic aspects of depression and the caregiver burden. "Negative beliefs about worry regarding the uncontrollability and danger," showed the strongest correlations to all the above-mentioned aspects. The negative beliefs showed the strongest correlations to the maladaptive coping strategy.
Quattropani et al. (2018c)	Multiple sclerosis ($n = 50$) Healthy subjects ($n = 50$)	Cross-sectional	MCQ-30	The *T*-test for two independent samples (using the Bonferroni correction) showed insignificant differences for metacognitions between the MS patients and the healthy subjects. A positive and moderate correlation was found between "cognitive confidence" and depression for the MS patients, but not for the control subjects. The negative beliefs were positively correlated to depression in the MS patients, but not in the control subjects. Moderate positive correlation between "cognitive self-consciousness" and depression was observed in the control subjects, but not in the MS patients.
Quattropani et al. (2017a)	Breast cancer subjects undergoing chemotherapy ($n = 80$)	Cross-sectional	MCQ-30	The results of the regression analysis has shown that the negative beliefs were significantly associated to anxiety, depression and overall distress.

(Continued)

TABLE 1 | Continued

Study	Clinical sample	Study design	MC tool	Main findings
Quattropani et al. (2016)	Cancer patients undergoing chemotherapy ($n = 175$)	Cross-sectional	MCQ-30	The negative beliefs had the strongest correlation to both anxiety ($r = 0.74$; $p < 0.01$) and depression ($r = 0.58$; $p < 0.01$). The cognitive confidence showed low correlation coefficients to anxiety ($r = 0.24$; $p < 0.01$) and depression ($r = 0.22$; $p < 0.01$). The positive beliefs had a low significant correlation to anxiety ($r = 0.20$; $p < 0.05$), but not to depression. The total score of the MCQ was positively related to all the other observed variables.
Strodl et al. (2015)	HIV community subjects ($n = 106$)	Cross-sectional	MCQ-30	The Negative Metacognitive Beliefs was the only metacognitive beliefs involved in the relationship between the HIV stigma perceptions and the depressive and anxious symptoms.
Toffalini et al. (2015)	Parents of children with cancer ($n = 30$) Hospitalized control parents ($n = 36$) Healthy control parents ($n = 30$)	Cross-sectional Controlled	MCQ-30	The parents in both the study group and the hospitalized control group reported less SWB than the healthy control group. Metacognition explained up to 77% of the variance in the SWB in the parents of children with cancer, compared to only 23% in the hospitalized control group and 33% in the healthy control group.
Ziadni et al. (2018)	Chronic pain ($n = 211$)	Cross-sectional (2 weeks)	MCQ-30	The participants with higher average levels of daily pain intensity and the negative metacognitive beliefs about worry reported higher levels of daily pain catastrophizing, as well as daily depression, and anxiety. Some aspects of the metacognitive beliefs (i.e., dangerousness and the uncontrollability of thoughts) were also negatively associated to the average daily levels of positive effects. However, these effects were not interactive; the metacognitive beliefs did not moderate the relationships of pain catastrophizing with the other daily variables.

and maladaptive metacognitive beliefs in cancer survivors (Fisher et al., 2017, 2019).

We retrieved only one study that investigated the impact of metacognition in parents of children with cancer, suggesting that metacognitive beliefs might be related to the development of psychological distress and emotional disorders not only in cancer patients but also in caregivers (Toffalini et al., 2015). The authors showed that the parents of such children exhibited worse self-well-being compared to the control parents. Specifically, the dysfunctional metacognitive factors explained a higher variance of self-well-being in the parents of children with cancer, compared to the parents of healthy children, as well as the parents of hospitalized children.

Metacognition in Post-stroke Patients

The connection between metacognition and mood has been broadly investigated in several medical conditions related to psychological comorbidity. However, the study conducted by Donnellan et al. (2016) represents the first attempt to describe this connection in post-stroke patients. Patients experiencing post-stroke anxiety and depression symptoms also show stronger metacognitive beliefs regarding cognitive confidence, cognitive self-consciousness, uncontrollability, and danger. According to the authors' conclusions, this metacognitive profile may affect both the patient's cognitive processing and actions, consequently worsening the psychological distress.

The MCQ-30 proved to be a valuable tool in assessing the metacognition in a stroke cohort, even though the small sample size did not permit further examinations.

Metacognition and Parkinson's Disease

Parkinson's disease (PD) is frequently associated with several psychological burdens, often shared between patients and their caregivers. The hypothesis stating that metacognitive beliefs may affect the modalities of how patients adapt to the disease has been recently tested.

The dysfunctional metacognitive style was found to be independently associated with increased distress in patients with PD (Allott et al., 2005). Moreover, the authors suggested that subjects who exhibit stronger negative beliefs about worrying may report elevated levels of distress.

Further considerations about the role of metacognition in PD have been recently discussed by Brown and Fernie (2015). The authors confirmed that dysfunctional metacognitive beliefs are associated with the worsening of anxiety levels in PD patients. They also suggested, for the first time, that metacognition might be also independently associated with the development of the off period distress.

Metacognition and Chronic Fatigue Syndrome (CFS)

Several studies have previously investigated the impact of psychological factors in subjects affected by CFS, highlighting that anxiety, depression, and stress are commonly associated with this condition (Afari and Buchwald, 2003). The potential role

TABLE 2 | Quality assessment of included cross sectional studies.

Study	Selection	Comprability	Outcome	NOS stars
Allott et al. (2005)	***	*	*	5
Brown and Fernie (2015)	***	**	*	6
Butow et al. (2015)	***	**	*	6
Cook et al. (2014a)	***	**	*	6
Cook et al. (2014b)	***	**	*	6
Cook et al. (2015)	***	**	*	6
Donnellan et al. (2016)	***	**	*	6
Fisher et al. (2018a)	****	**	*	6
Fisher et al. (2015)	***	**	*	6
Fisher et al. (2017)	***	**	*	6
Fisher et al. (2016)	***	**	*	6
Gill et al. (2015)	***	**	*	6
Heffer-Rahn and Fisher (2018)	**	**	*	5
Jacobsen et al. (2016)	**	**	*	5
La Foresta et al. (2015)	***	**	*	6
Maher-Edwards et al. (2011)	***	**	*	6
Purewal and Fisher (2018)	**	**	*	5
Quattropani et al. (2018d)	***	**	*	6
Quattropani et al. (2018c)	***	**	*	6
Quattropani et al. (2017a)	***	*	*	5
Quattropani et al. (2016)	***	**	*	6
Strodl et al. (2015)	***	**	*	6
Ziadni et al. (2018)	***	**	*	6

NOS, Newcastle Ottawa Scale. An adapted NOS for cross-sectional was employed. Each study can be awarded of a maximum of ten NOS stars.

TABLE 3 | Quality assessment of included case-controlled studies.

Study	Selection	Comprability	Exposure	NOS stars
Bagcioglu et al. (2012)	***	*	**	6
Fernie et al. (2015)	**	**	**	6
Mutlu et al. (2018)	***	**	**	7
Toffalini et al. (2015)	***	**	**	7

NOS, Newcastle Ottawa Scale. Each study can be awarded of a maximum of nine NOS stars.

of metacognition has also been investigated owing to its known association with negative emotions.

Metacognitive beliefs, particularly negative beliefs about thoughts regarding uncontrollability, cognitive confidence, and beliefs about the need to control one's thoughts, might be independently correlated to symptom severity in CFS, regardless of the negative emotions (Maher-Edwards et al., 2011). In this cross-sectional study, the authors for the first time showed that metacognition was a better independent factor associated with physical and psychological symptom severity than anxiety and depression.

Metacognitive beliefs were also recently found to have a significant effect on fatigue severity even across the commonly used treatment modalities, such as cognitive behavioral therapy (CBT) and graded exercise therapy (GET). The authors discussed that the relation between metacognition and fatigue could be mediated by CBT, since metacognition is an indirectly addressed variable in CBT programs. On the other hand, they suggested that the relationship between metacognitive beliefs and the changes in fatigue severity might reflect decreased worry and symptom preoccupation, which are variables that have been shown to mediate the outcomes in GET (Fernie et al., 2015).

Another recent study reported for the first time the associations between dysfunctional metacognitive beliefs and subjective cognitive impairments in CFS patients (Jacobsen et al., 2016). Specifically, the baseline scores on the subscale of cognitive confidence were independently associated with the subjective cognitive impairment at the end of an occupational therapy-based intervention (Return-To-Work, RTW). Moreover, a reduction in dysfunctional cognitive confidence while undergoing treatment was found to be associated with less subjective cognitive impairments at the end of the RTW intervention.

Metacognition and Epilepsy

The investigation of metacognition in subjects affected by epilepsy was aimed at achieving a better conceptualization of the psychological mechanisms that contribute to anxiety and depression, which are commonly related to this condition. The MCQ-30 was previously validated as a valuable measure of metacognitive beliefs, with a substantial clinical utility within subjects with epilepsy (Fisher et al., 2016).

The potential role of the metacognition model in explaining anxiety and depression in subjects suffering from epilepsy was recently investigated for the first time (Fisher and Noble, 2017). The authors showed that negative metacognitive beliefs about the uncontrollability and the dangers of worrying were independently associated with the symptoms of anxiety and depression. Furthermore, it was highlighted that metacognitions also explained additional variance in anxiety and depression independently of demographic characteristics, epilepsy-related variables, and the patients' illness perception (Fisher et al., 2018b).

Metacognition and Acquired Brain Injury (ABI)

Metacognition was recently investigated as a potential mediator of PTSS severity in individuals with Acquired Brain Injury (ABI) (Gill et al., 2015). Authors supported the application of a novel metacognitive model of PTSD for those with an ABI. The study highlighted that the negative beliefs about the uncontrollability and the dangers of worrying, as well as the beliefs about the need to control one's thoughts, were independently associated with the PTSS severity in subjects after a brain injury.

Metacognition and Multiple Sclerosis (MS)

Metacognitive beliefs were previously associated with emotional distress in neurological conditions. A recent study (Heffer-Rahn and Fisher, 2018) for the first time investigated the potential role of metacognitive beliefs in patients with MS. The authors showed that the positive beliefs about worry, the negative beliefs about the uncontrollability and the dangerous nature of worry, the cognitive confidence, and the need to control one's thoughts were positively associated with distress. Furthermore, metacognition

independently explained the additional variance in the distress of the patients with MS.

Some interesting results have been discussed in an equally recent case-controlled study (Quattropani et al., 2018c) aimed at examining the relationships between metacognition, anxiety, and depression in MS patients and healthy subjects. This is the first controlled study exploring metacognition in MS patients. The authors indicated that patients and healthy controls showed no significant differences in terms of metacognitive beliefs. According to an authors' discussion, a suggested role of metacognitions as vulnerability factors in predicting the development of psychological symptoms would explain their findings, even though further investigation would be needed.

Moreover, the cognitive confidence, positive beliefs, negative beliefs, and the need to control one's thoughts were positively correlated to anxiety and the overall distress in both MS patients and healthy subjects. However, the association between these metacognitive factors and depression was conflicting in patients and controls, with the positive correlations only seen in the patients. According to the authors, these evidence might suggest a different impact of metacognition on the distress variables between the MS patients and healthy subjects.

Metacognition and Amyotrophic Lateral Sclerosis (ALS)

The role of metacognitive factors among caregivers is a research topic not usually investigated, at least in the context of medical conditions. In this regard, the assessment of metacognition in the ALS patients' caregivers represents a recently explored field.

Our systematic search retrieved the first multicentric study (Quattropani et al., 2018d) which indicated dysfunctional metacognitive beliefs (namely, negative beliefs about worry, about uncontrollability, and danger) as being significantly related to state and trait anxiety, depression, and to the status of burden in the ALS patients' caregivers. The authors highlighted the relevance of exploring metacognitive factors in caregivers in order to identify profiles potentially at risk of developing distress and other burden-related symptoms.

Metacognitive beliefs have also been studied in ALS patients' caregivers as factors potentially involved in executive functions (EF) regulation, since caregiving requires abilities such as cognitive flexibility, self-regulation, and self-consciousness, which are commonly related to both metacognitive processes and executive functioning (La Foresta et al., 2015). The authors effectively discussed the relationship between metacognitive factors and perseveration exhibited on the Wisconsin Card Sorting Test, used to assess EF. According to the authors, this finding suggests that the tendency to perseverate could be closely linked to dysfunctional metacognitive beliefs, as an expression of a specific inflexibility in thinking processes.

Metacognition and Diabetes

Only one study investigating metacognitive beliefs in subjects with diabetes met the required inclusion criteria for our systematic review. Anxiety and depression are common in people with diabetes. According to Purewal and Fisher (2018), metacognition is a factor capable of explaining anxiety and depression, independently of demographic characteristics and illness perception. The negative beliefs about the uncontrollability and the dangers of worrying, and a lack of cognitive confidence, appeared to be the most significant metacognitive factors associated with anxiety and depression.

Metacognition and Chronic Pain

Metacognitive beliefs have recently been indicated as factors independently associated with pain and its impact on daily functioning among subjects suffering from Chronic Pain (CP) (Ziadni et al., 2018). Particularly, the authors showed that the metacognitive beliefs about the uncontrollability and the danger of thoughts, as well as those related to self-consciousness, were independently related to the daily levels of psychological functioning. However, none of the metacognitive factors were able to modify the intensity of the relationships between pain catastrophizing and emotional conditions. Therefore, the authors suggest that metacognitive beliefs might be considered as an index of poor psychological adjustment to chronic pain, rather than a risk factor which amplifies the immediate negative consequences of catastrophizing.

Metacognition, HIV, and Sexual Dysfunction

The investigation of the potential role of metacognition eventually included HIV and Sexual Dysfunctions.

Subjects with HIV show stronger negative metacognitive beliefs, which are significantly associated with their anxiety and depression symptoms, and to the increased psychological distress resulting from the disease-related stigma (Strodl et al., 2015).

Patients with sexual dysfunctions seem to focus on the metacognitive belief that worrying could have positive effects in solving problems and avoiding unpleasant situations which are associated with sexual disorders (Bagcioglu et al., 2012).

DISCUSSION

Summary of Main Findings

As per our understanding, this is the first attempt to systematically review the studies aimed at investigating metacognitive beliefs in patients with chronic medical conditions and their caregivers. Particularly, the dysfunctional metacognitive factors according to the S-REF model and their relationships with both emotional and psychological distress were investigated.

We have focused our research on metacognition as postulated by Wells, who emphasized how metacognitive processes might incline individuals toward developing response patterns to perceived cognitive, behavioral, or emotional difficulties (Wells, 2000b). In light of this perspective, the Metacognitions Questionnaire (MCQ) and its short version (MCQ-30) have been considered as reliable measures of metacognitive beliefs and processes.

Metacognition has been originally defined as, "the aspect of information processing that monitors, interprets, evaluates, and regulates the contents and processes of its organization." (Wells and Purdon, 1999). Owing to its association to the development and maintenance of psychological dysfunctions, metacognitive

beliefs have been broadly investigated in the context of both non-clinical (Spada et al., 2008b) and psychiatric samples (Sellers et al., 2016; Sun et al., 2017).

In recent decades, the study of metacognition has also extended to patients suffering from different medical conditions, which negatively affected their quality of life and exposed them to psychological distress.

The studies included in this systematic review have mostly considered different chronic medical conditions, such as cancer and neurological diseases. Metacognition has been specifically explored in those medical conditions which are often related to increased anxiety and depression, with negative effects on patient's quality of life. The majority of these diseases seem to exhibit a metacognitive profile mainly characterized by the presence of negative beliefs factors, which have been described as significantly associated with emotional and psychological distress. In this regard, negative beliefs about worry, its uncontrollability, and dangers seem to represent a common metacognitive pattern across the investigated pathologies, even when motor dysfunctions are involved (as in Parkinson's off-periods).

In the context of the investigated medical conditions, it has been shown that living with cancer and surviving cancer might lead to the development of dysfunctional negative beliefs about a patient's future, as well as to the development of PTSS. In this context, MCT has been described as a valid intervention that reduces both the emotional distress and the fear of recurrence in cancer survivors.

In addition to the evidenced general pre-disposition to exhibit negative beliefs, cognitive confidence has been described as another relevant factor. It is a measure of an individual's confidence in his own attention and memory. It has been found being associated with psychological and emotional distress, and it might negatively affect coping strategies when the patient feels mentally fatigued (as in neurological conditions, cancer, or chronic fatigue).

Finally, an important issue is the role of metacognition among caregivers of subjects affected by a chronic illness. The patients' caregivers are often exposed to a high risk of emotional and psychological burden, particularly in relation to the degree of the patient's behavioral or physical impairment. However, only two studies have been retrieved investigating the metacognition in caregivers, and they specifically involved the parents of children with cancer and the caregivers of ALS patients. In this context, metacognitive beliefs seem to be involved in emotional distress even in caregivers. Further studies offering an insight on the role of metacognitive beliefs in caregivers are needed in order to better characterize psychological distress in caregivers.

In this regard, a recent study on a sample of health care professionals provided evidence on the differential role of metacognitions in predicting the risk of burnout (Quattropani et al., 2017b).

Limitations

While included studies showed an adequate quality as evidenced through the NOS assessment, most of them presented some methodological weaknesses.

The majority of studies adopted a cross-sectional design, which does not allow for inferences of causality. Furthermore, the majority of the reviewed studies did not involve a control sample or other conditions for comparison. In addition, the absence of a control sample could make it difficult to attribute the findings to that specific medical condition.

Finally, only a limited number of studies reported temporal variations of metacognitive factors evaluation, adopting follow-up observations. Longitudinal studies are strongly needed and recommended in order to deepen understanding of the impact of dysfunctional metacognitive beliefs on psychological and emotional distress. Additionally, longitudinal observations would better clarify the potential efficacy of psychological intervention based on metacognition.

Conclusions

The findings of this systematic review provide evidence that dysfunctional metacognitive beliefs are significantly associated with emotional and psychological distress in patients with medical chronic conditions, and caregivers. Therefore, within the compendium of psychological assessments usually performed in the context of medical chronic conditions, even the additional evaluation of metacognitive factors appears valuable.

Based on the evidenced association between metacognition and negative emotions, psychological interventions centered on the metacognitive approach (Wells, 2000b) could have positive effects on emotional and psychological distress in patients with chronic medical conditions, and their caregivers.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author

AUTHOR CONTRIBUTIONS

MQ and VL contributed to the conception of this systematic review. VL and AS performed the literature search and wrote the first draft of the manuscript. MQ and GM revised the first draft of the manuscript. All authors contributed to the subsequent drafting and rewriting of the manuscript and approved the final version of the manuscript.

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ORIGINAL RESEARCH
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Going Beyond the Visible in Type 2 Diabetes Mellitus: Defense Mechanisms and Their Associations With Depression and Health-Related Quality of Life

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Introduction: Clinical psychological features may impact a person's aptitude to deal with chronic diseases, leading to emotional distress, suffering, and a worse perceived quality of life (QoL). Chronic diseases are largely represented, and their incidence is constantly increasing all over the world. Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic diseases and it is very difficult to manage, demanding long term self-management, which improves the perceived QoL. The aim of this study was to explore defense mechanisms, depression, QoL, time since diagnosis, and metabolic control in T2DM patients.

Methods: 51 patients with T2DM were assessed through a psychodiagnostic battery: Beck Depression Inventory-II, the 36-Item Short Form Health Survey, including indexes of Physical and Mental Component Summary and the Defense Mechanisms Inventory. Times since DM diagnosis and glycated hemoglobin values were detected.

Results: Participants were mainly female (62.74%), with a mean age of 66.1 years. T2DM time since diagnosis was 11.77 years (SD = 7.1). Mild depression was detected (with an overall score between 13 and 19). *Projection* was significantly associated with higher depression and with lower physical well-being; *Principalization* was negatively associated with depression and positively with both physical and mental well-being. *Turning Against Self* correlated positively with physical well-being and negatively with mental well-being. *Reversal* was associated with lower depression and higher mental well-being. A negative high correlation emerged between depression and mental well-being. Finally, a significant relationship was found between Projection and higher time since diagnosis ($r = 0.31$, $p < 0.05$).

Conclusion: The correlations between defense mechanisms, depression and health-related QoL highlight the potential personification and protagonization, which may increase over time due to the illness intrusiveness and worsening of diabetes symptoms. The positive association between defensive strategies and well-being measures should be cautiously considered.

Keywords: defense mechanisms, depression, quality of life, physical component summary, mental component summary, chronic diseases, type 2 diabetes mellitus

INTRODUCTION

Clinical psychological features may impact a person's aptitude to deal with chronic diseases, which may lead to emotional distress, suffering, and a worse perceived quality of life (QoL). Chronic diseases are largely represented among the general population, and their incidence is constantly increasing all over the world. It has been recognized that affective and emotional symptoms, such as depression and anxiety, respectively, could embody predictors of several chronic diseases (Conversano et al., 2015; Catalano et al., 2017, 2018; Martino et al., 2018a,b, 2019b,a; Kelly et al., 2019; Marchi et al., 2019). Particularly, psychological factors may compromise patients' compliance and adherence, and this could increase mortality and mobility independently from many confounders (Wang et al., 2016). It is known that diabetes is one of the most common chronic diseases in the world and it is very difficult to manage, demanding long term self-management through constant blood glucose monitoring, a balanced diet, physical exercises and medical treatment, which improve perceived QoL (Conversano et al., 2009; Veltri et al., 2012; Palagini et al., 2016; Marchini et al., 2018; Catalano et al., 2019b; Conversano, 2019; Guicciardi et al., 2019; Martino et al., 2019d,c; Merlo, 2019; Quattropani et al., 2019; Lenzo et al., 2020). In fact, both adequate compliance and adherence prevent its relative outcomes leading to a lower risk of developing related complications (American Diabetes Association, 2018). Due to this, self-care could be considered as a suggestive index of patients' adaptation to diabetes, which may involve psychological adjustment to disease and its related emotional distress (Lapolla et al., 2012; Schmitt et al., 2014; Del Piccolo et al., 2015; Craparo et al., 2016; Settineri et al., 2019a,b; Knowles et al., 2020). Emotional distress could exist independently from such chronic disease, though considering the higher risk of mortality and morbidity due to diabetes, a psychological elaboration processing would be useful for the psychic integration of the chronic illness experience within patients' daily life (Whittemore et al., 2010; Castelnuovo et al., 2015; Van Houtum et al., 2015; Stanton and Hoyt, 2017; Di Giuseppe et al., 2018, 2019; Savarese et al., 2018; Catalano et al., 2019a). Demographical and physical characteristics, such as body mass index (BMI) and smoking and alcohol consumption, could predict depression in Type 2 Diabetes Mellitus (T2DM) (Bouwman et al., 2010; Rosa et al., 2019). Smith et al. (2013) observed a significant correlation between diabetes, anxiety symptoms and anxiety disorders, and highlighted that a fruitful psychological adjustment to diabetes is significantly associated with a better metabolic control, self-care and higher QoL. Moreover, controversial data support T2DM as a relevant risk factor for anxiety and highlight that good health, in the absence of T2DM, could represent a protective factor for anxiety. Martino et al. (2019b) underlined the predictive role of anxiety levels and disease duration in health related QoL in patients living with T2DM. Particularly, they observed a significant impact of time since diagnosis on Physical Component Summary (PCS) and a higher significant impact of anxiety and depression levels on both PCS and Mental Component Summary (MCS). The role of negative emotions and illness distress is deemed relevant for both the course and treatment efficacy in patients with T2DM (Heianza et al., 2015). In this regard, it is well acknowledged that feelings of loss, guilt and anger are associated with both worse glycemic control and indicators of medical adherence, such as glycated hemoglobin levels (Whithorth et al., 2016). Therefore, the need for further clinical psychological research is advocated in order to explore less conscious strategies to handle such a chronic condition (Pouwer et al., 2010; Marchini et al., 2018).

In line with these pieces of research based on the fundamental role of personal adjustment to such a chronic illness related to both psychological and physical health status, the aim of this study was to explore the relationships between defense mechanisms and depression, perceived QoL, time since diagnosis, and metabolic control in patients with T2DM.

MATERIALS AND METHODS

Participants

A convenience sample of 51 patients was recruited at the Outpatients Clinics of the Department of Clinical and Experimental Medicine, University Hospital of Messina, Italy. Enrolled patients had a certified diagnosis of T2DM, in agreement with the American Diabetes Association criteria (American Diabetes Association, 2018), and they satisfied inclusion and exclusion criteria before entering the study. Inclusion criteria were: age from 55 to 75 years old; time since diagnosis of T2DM >5 years; pharmacological treatment with hypoglycemic drug (Metformin) and adequate schedules in the last 12 months; a full screening for diabetic outcomes over the last 6 months; a Mini-Mental State Examination score (MMSE) >24, to ensure the full comprehension of the psychodiagnostic evaluation. The exclusion criteria were: neurologic or psychiatric condition or use of neuropsychotropic drugs; heart failure as New York Heart Association (NYHA) class >2; respiratory, kidney or liver failure higher than moderate; endocrine disorders

other than DM, to avoid confounders; severe musculoskeletal diseases; cancer.

Ethics Statement

The study was approved by the Institutional Ethical Committee of the University Hospital "G. Martino," University of Messina, Italy. All participants were fully informed about the purpose of the research and gave their written informed consent, in accordance with the Declaration of Helsinki and its later amendments. Participants were evaluated by a researcher in clinical psychology and physicians. Data were analyzed anonymously.

MEASURES

Demographical and Clinical Data

Collected demographical data included: age, gender, education, smoking habits, and employment, considered as categorical variables. Medical information covered data on BMI, T2DM duration and related outcomes, and metabolic control.

Clinical Psychological Evaluation

Clinical psychological assessment was performed through a gold standard psychological interview by a researcher in clinical psychology, in a confidential setting, to detect patients' mental status (Fava et al., 2012; Langher et al., 2017). The gold standard interview was implemented with the administration of self-report tests, inventories and questionnaires.

Particularly, the Beck Depression Inventory - second edition (BDI-II) was administered to identify depressive symptoms. It consists of 21 items scored on a 3-points Likert scale from 0, not present, to 3, severe (Beck et al., 1996; Ghisi et al., 2006). In the present study, the reliability (Cronbach's α) of the measure was 0.85.

The Italian version of the Short Form-36 (SF-36) (Ware and Sherbourne, 1992; Apolone and Mosconi, 1998) was used to measure patients' perceived health-related QoL. SF-36 comprises eight domains, measuring perceived mental health, role emotional, social functioning, vitality, general health, bodily pain, role physical, physical functioning. This self-report questionnaire has a total score ranging from 0 to 100 points with lower scores suggesting a worse perceived QoL. It permits the appraisal of patients' health status through two synthetic indexes, PCS and MCS, reflecting physical and mental well-being respectively. The scoring algorithm for PCS embraces physical functioning, role physical, bodily pain, general health, and vitality scales, while the scoring algorithm for MCS includes vitality, social functioning, role emotional, and emotional well-being scales. In the present study, the reliability (Cronbach's α) of the measure was 0.69 and 0.79 for PCS and MCS respectively.

The Defense Mechanisms Inventory (DMI) (Gleser and Ihilevich, 1969; Ihilevich and Gleser, 1986, 1994) is a semi-projective questionnaire, which encourages the subject to identify him/herself with ten short semi-structured stories, detecting both the presence and uniformity of five defensive clusters. Particularly, it consists of two stories for each area of investigation, namely: authority, independence, masculinity or femininity, competition, and finally, the area of conflicts which arise in daily life experiences. Each story comprises 20 likely answers distributed into four groups. The first group embraces "items" investigating behavior in realistic situations, the second includes impulsive behavior, the third comprises thoughts, and the fourth group holds affects. The five defense styles explore: Turning Against Object (TAO), as aggression in terms of identification with the aggressor and displacement; Projection (PRO), as the justification of aggression against the considered object; Principalization (PRN), as isolation, rationalization and intellectualization; Turning Against Self (TAS), as aggression against the self in terms of masochism and introjection; and Reversal (REV), as repression, denial and reaction formation. In the present study, the reliability of the measure for each scale was as follows: TAO (α = 0.72), PRO (α = 0.69), PRN (α = 0.65), TAS (α = 0.71), REV (α = 0.70).

Clinical Characteristics

Physical evaluation was performed, determining height, weight, and BMI, expressed as weight in kilograms divided by the square of height in meters (Kg/m^2). The detection of glycated hemoglobin (HbA1c), expressed as per cent values (%), reveals the mean blood glucose concentration in the last 3 months offering fundamental data on patients' metabolic control. T2DM pharmacological treatment and T2DM related outcomes, such as hypertension and atherosclerosis nephropathy, retinopathy, glaucoma, and neuropathy, were collected during the clinical interview and derived from patients' medical records.

Statistical Analysis

Statistical analysis was performed using IBM SPSS statistical version 25. Descriptive analyses were completed concerning the demographic variables and clinical psychological dimensions. Clinical psychological variables for DMI, BDI-II, PCS, and MCS were normally distributed. Pearson's *r* correlations were performed to evaluate the relationships between defense mechanisms and both depression and perceived QoL. Moreover, the relationships between defense mechanisms, time since diagnosis and metabolic control were examined. p values <0.05 were considered as statistically significant.

RESULTS

The recruited 51 participants were mainly female (62.74%), with a mean age of 66.1 years (SD = 6.1), and a secondary or higher education in most cases (overall 77.84%). Concerning T2DM, on average, time since diagnosis was 11.77 years (SD = 7.1), and related complications were reported only in 30% of participants, who showed a good glycemic control overall. The clinical sample characteristics are reported in **Table 1**.

Descriptive statistics of the study variables are shown in **Table 2**. Looking at the mean values of the defense mechanisms examined through DMI, compared to norms differentiated by gender of the Italian sample (Ihilevich and Gleser, 1994), Principalization was higher than one standard deviation in male

TABLE 1 | Demographic and medical characteristics of the study sample.

Variable		*Clinical sample (n = 51)*
Gender	M	37.25%
	F	62.74%
Education	Primary school	21.16%
	Secondary school	58.82%
	High school or higher degree	19.02%
T2DM time since diagnosis *(yrs)*		11.77 ± 7.1
HbA1c *(%)*		7.18 ± 0.9
T2DM related complications	Micro-vascular	15%
	Macro-vascular	15%
Age *(yrs)*		66.1 ± 6.1
BMI *(Kg/m^2)*		29.9 ± 5.2
Current smoking		15%

TABLE 2 | Descriptive statistic of the study variables.

Measure	Mean	SD
TAO	42.54	11.79
PRO	50.59	8.55
PRN	50.66	8.09
TAS	49.24	8.56
REV	59.93	11.28
BDI-II	15.15	8.96
PCS	37.68	9.41
MCS	39.32	12.29

TAO, Turning against object; PRO, Projection; PRN, Principalization; TAS, Turning against self; REV, Reversal; BDI-II, Beck depression inventory-II; PCS, Physical component summary; MCS, Mental component summary.

participants (normative mean of 44.9 with a standard deviation of 7.8). Moreover, TAS and Reversal were found to be higher in both males (whose normative values were, respectively, $M = 34.5$, SD = 8.8 for TAS and $M = 37.1$, SD = 7.7 for REV) and females (whose normative values were, respectively, $M = 33.5$, SD = 8.1 for TAS and $M = 30$, SD = 7.6 for REV). According to the norms of the BDI-II in the Italian context (Ghisi et al., 2006), the present sample was characterized by mild depression (with an overall score between 13 and 19). With regard to health-related QoL, both PCS and MCS have values expressed in t-scores ($M = 50$, SD = 10) below one standard deviation from the mean, and lower than those of the Italian normative sample (Apolone and Mosconi, 1998).

The interrelations among the study variables are shown in **Table 3**. With regard to defense mechanisms, some statistically significant associations were found, demonstrating an overall fall in medium size range. Specifically, Projection was associated with higher depression and with lower physical well-being, whereas, Principalization was negatively associated with depression and positively associated with both physical and mental well-being. TAS correlated positively with physical well-being and negatively with mental well-being. Further, Reversal was associated with lower depression and higher mental well-being.

TABLE 3 | Interrelations among the study variables.

	TAO	PRO	PRN	TAS	REV	BDI-II	PCS	MCS
TAO	–	–	–	–	–	–	–	–
PRO	0.40**	–	–	–	–	–	–	–
PRN	−0.70***	−0.62***	–	–	–	–	–	–
TAS	−0.41**	−0.32*	0.09	–	–	–	–	–
REV	−0.76***	−0.57***	0.55***	0.02	–	–	–	–
BDI-II	0.26	0.38*	−0.52***	0.30	−0.43**	–	–	–
PCS	−0.20	−0.34*	0.33*	0.33*	0.13	−0.17	–	–
MCS	−0.23	0.00	0.31*	−0.38*	0.37*	−0.59***	0.04	–

*TAO, Turning against object; PRO, Projection; PRN, Principalization; TAS, Turning against self; REV, Reversal; BDI-II, Beck depression inventory-II; PCS, Physical component summary; MCS, Mental component summary. *statistically significant at $p < 0.05$, **statistically significant at $p < 0.01$, ***statistically significant at $p < 0.001$.*

A negative high correlation also emerged between depression and mental well-being.

With regards to the associations between defense mechanisms and both time since diagnosis and metabolic control in patients with T2DM, the only statistically significant relationship was found between Projection and higher time since diagnosis ($r = 0.31$, $p < 0.05$).

DISCUSSION

It is acknowledged that T2DM may incite distress, as patients suffer with a need to self-manage such chronic disease, recurrently detect blood glucose levels, and show adequate compliance adherence (Marshall et al., 1997; Marchini et al., 2018), which facilitate the avoidance of unhealthy behavior and outcomes. It is also known that people with psychopathological features showed an amplified risk to develop T2DM onset at a 10-year follow-up, independently from conventional risk factors for DM (Engum, 2007; Shinkov et al., 2018).

Overall, compared to normal samples, the study participants seem to be characterized by a mild level of depressive symptoms, worse perceived QoL in both physical and mental terms, and a higher proneness to use some defense mechanisms, thus highlighting the underlying psychic suffering intertwined with T2DM.

With regards to the associations between defense mechanisms and both depression and health-related QoL, the present study highlights interesting findings in participants with T2DM. In more detail, Projection is found to be associated with higher depression, thus suggesting that depressive symptoms in such a sample are higher when there is a greater tendency to attribute negative characteristics or intent to an external object without unequivocal evidence. Therefore, from a psychodynamic perspective, it can be hypothesized that psychic processes of personification and protagonization of illness are strongly intertwined with depression in chronic diseases (Schattner et al., 2008; Shahar and Lerman, 2013). Indeed, people with diabetes may perceive their chronic illness as a sort of "bad" persecutory object (Marchini et al., 2018), ascribing human attributes to their stressful condition as a separate entity

(Shahar and Lerman, 2013). This is confirmed by the association between Projection and lower physical well-being found in the present study. Indeed, diabetes-related limitations and poorer physical status may intensify the perceived illness intrusiveness and the consequent tendency to rely on Projection, thus externalizing the responsibility of care management (D'Alberton et al., 2012; Caputo, 2013; Conti et al., 2016; Marchini et al., 2018). Besides, as Projection involves the justification of aggression against external sources of frustration, such a defense mechanism might lead to the justifying of covert hostile and counter dependent behaviors, such as a bad lifestyle and reduced treatment adherence, in turn negatively affecting one's physical status. This is in line with previous findings regarding the high levels of frustration and anger in patients with T2DM, mainly due to restrictions on food and comorbidities in sexual life (Zurita-Cruz et al., 2018; Al Anazi et al., 2019).

Another interesting finding refers to Principalization, which is associated with lower depression and better QoL in both physical and mental components. This is consistent with the tendency to repress negative affect, which is typical of Principalization, overall resulting in the improvement of personal well-being. In this regard, several interpretations can be made. On the one hand, Principalization may work as a protective factor against experiencing diabetes distress, thus enacting more rational explanations for such a chronic condition and more effective strategies to handle it without feeling powerless and overwhelmed. In this sense, according to the theoretical framework, it would contribute to the modulation of the experience and the expression of anger, thus reducing negative affect reactivity to daily stressors (McIntyre et al., 2019; Vicario et al., 2019). However, on the other hand, as Principalization involves the splitting of thought content from affect, it could lead to unresolved or denied depression that may have a negative impact in chronic diseases in the long run (Hyphantis et al., 2005).

Aside from this, some conflicting findings emerge with regards to TAS, as such a mechanism correlates positively with physical well-being and negatively with mental well-being. Despite their seeming counterintuitive associations, the sense of guilt can be advocated as a fruitful construct for their understanding. Indeed, the tendency to handle diabetes-related conflicts by directing aggressiveness toward oneself may trigger self-punishment thoughts referring to a persistent sense of self-defectiveness, thus negatively affecting mental well-being. At the same time, self-blame for having symbolically damaged one's health status may increase the effort in reparation, for example by adopting the correct lifestyle behaviors, monitoring blood glucose and complying with a medical regimen, which contribute to the improvement of one's physical health status (Marchini et al., 2018).

Furthermore, Reversal, including defenses that act to minimize the severity of perceived threats by responding neutrally or positively toward a frustrating object, was found to be associated with lower depression and higher mental well-being. This result is not surprising, as denial-related defenses aimed at lessening one's sense of loss are demonstrated to contribute to diabetes adaption to some extent (Marchini et al., 2018), as a way of contrasting the process of somatic disruption (Caputo, 2019a). Several authors have stated that denial may serve as an emotion-focused coping strategy, allowing the reduction of distress perception in patients with diabetes in the short term (Gois et al., 2012; Tripathy et al., 2012; Marchini et al., 2018). However, it should be noted that such a defensive strategy does not necessarily lead to effective self-care behaviors (Hyphantis et al., 2005; Marchini et al., 2018; Caputo, 2019b), as also suggested by the lack of association with physical well-being in the present study.

The findings regarding the potential correlations between defense mechanisms and both time since diagnosis and metabolic control show no significant associations, with the exception of a positive relationship between Projection and time since diagnosis. This result seems to provide further confirmation about the processes of personification and protagonization of diabetes, as the worsening of such a chronic condition over time is intertwined with the increase of aggression toward an external object that is attributed with negative characteristics (Schattner et al., 2008; Shahar and Lerman, 2013; Marchini et al., 2018).

The added value of the current study is the exploration of defense mechanisms as less conscious variables that could potentially affect personal adjustment to a chronic illness, as in the case of T2DM, that are scarcely investigated in the clinical psychological literature. Another strength is the use of a diagnostic interview, in addition to self-report measures, which can be considered as a gold standard, conferring more robustness to the surveys carried out.

However, some study limitations should be acknowledged, such as its cross-sectional nature, the small sample size and the consequent reduced generalizability of the findings. As potential causal relations among the examined variables cannot be inferred, future research could assess the impact of the considered defensive mechanisms in longitudinal studies, including participants with T2DM. Moreover, the results seem to be very promising, based on the size of some correlational index, even if the high correlations among the DMI's scales could need more investigation in regard to the structural power of this instrument. Aside from this, the inspection of other potential unobserved variables or confounders affecting the detected relations could be proposed, as well as the inclusion of larger samples allowing sub-group analysis for the observation of specific differences (i.e. gender).

CONCLUSION

The present study suggests the potential relevance of defense strategies for the understanding of adaptation to chronic illness in patients with T2DM. Specifically, the study findings highlight that such a clinical sample is featured by a higher tendency to rely on defense mechanisms, probably due to the emotional suffering related to illness, as also confirmed by mild depressive symptoms and worse physical and mental well-being compared to Italian normative samples. The detected correlations between defense mechanisms and both depression and health-related QoL highlight the potential presence of

processes of personification and protagonization of diabetes, which may increase over time due to the illness intrusiveness and worsening of diabetes symptoms. Similarly, the positive association found between some defensive strategies (especially, Principalization and Reversal) and well-being measures should be cautiously considered because, despite reducing depressive feelings, they do not necessarily affect self-care and better medical adherence. These data could be expedient to project psychological strategies, specifically designed according to everyone's defense mechanisms and focused on psychological health concerns. Such psychological trajectories may support people living with T2DM, aiming at healthier self-management and at reducing both psychological and physical outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The study was approved by the Institutional Ethical Committee of the University Hospital "Gaetano Martino," University of Messina, Messina, Italy. Participants provided their written informed consent to participate in the study.

AUTHOR CONTRIBUTIONS

GM made significant contributions to the design of the research study, drafting of the manuscript, performing of the statistical analysis, interpretation of the data, and revision of the manuscript. AC performed the statistical analysis, provided the interpretation of data, and gave significant contribution to the draft part of the manuscript. FB provided substantial contribution in the drafting part of the manuscript. MQ critically revised the manuscript. CV critically revised the manuscript and gave the final approval of the manuscript to be submitted.

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MINI REVIEW
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Time Processing, Interoception, and Insula Activation: A Mini-Review on Clinical Disorders

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Time processing is a multifaceted skill crucial for managing different aspects of life. In the current work, we explored the relationship between interoception and time processing by examining research on clinical models. We investigated whether time processing deficits are associated with dysfunction of the interoceptive system and/or insular cortex activity, which is crucial in decoding internal body signaling. Furthermore, we explored whether insular activation predicts the subjective experience of time (i.e., the subjective duration of a target stimulus to be timed). Overall, our work suggests that alteration of the interoceptive system could be a common psychophysiological hallmark of mental disorders affected by time processing deficits.

Keywords: time processing, clinical disorders, interoception, insula, timing deficits

INTRODUCTION

The ability to track time is the result of a complex neural network, which includes a large set of cognitive and motor functions. A demonstration of the multidimensionality of timing ability is provided by the variety of terminologies associated with this mental function.

A classic distinction in the literature on time processing is made between prospective and retrospective timing (Block et al., 2018). The first involves advance knowledge of the duration of the target interval to be timed; the second implies that it is not known in advance that time of a target has to be estimated (Block et al., 2018).

A further element of time processing is the time scale of the phenomenon to be timed. In general, we distinguish between the ability to time sub-second and supra-second durations. These different temporal domains relate with the activity of segregated and relatively independent brain structures (see Ivry and Schlerf, 2008).

It is also important to distinguish between motor and perceptual timing. The first refers to the execution of a motor act to represent a temporal interval, as in the case of a time-line bisection task (e.g., Vicario, 2011), temporal production/reproduction (Vicario et al., 2011a,b), finger tapping (O'Regan et al., 2017), and movement synchronization (Vicario, 2012). The second involves a time comparison task, such as performing a task of discrimination between the duration of a reference and the duration of a target stimulus (e.g., Grondin et al., 1999; Vicario et al., 2009, 2012).

Finally, when it comes to timing, one could distinguish two dimensions, namely, time perception and time representation. The first refers to a synchronic (i.e., almost a real time) experience with the target to be timed. The second refers to diachronic (i.e., offline) experience with the target to be timed, that is, a timing that asks to make estimations about a target that was previously experienced or that is going to be experienced. With regard to time representation, making estimations about a target that was previously experienced requires a more direct involvement of memory processes, although it takes place also in the case of a target that is going to be experienced. In the second case, it is required to make predictions about the duration of the target to be timed, such as in the case of sports actions, where the accuracy in predicting the duration of a target (i.e., a moving ball) is crucial for successful sportive performance (Vicario et al., 2016).

The neural correlates of time processing include a wide range of cortical and subcortical structures, including the frontal and parietal cortex, the basal ganglia, the cerebellum, and the insula (for some reviews and discussion, see Ivry and Schlerf, 2008; Vicario and Martino, 2010; Vicario et al., 2013a,b; Bareš et al., 2019; Nani et al., 2019; Salehinejad et al., 2019, 2020). At the cognitive level, timing skills have been linked with attention, memory (Lewis and Miall, 2006), motor control (Avanzino et al., 2016), and interoception (Craig, 2009a; Meissner and Wittmann, 2011). Owing to this vast neural network, timing deficits are reported in various mental disorders (i.e., neurological and psychiatric), whose etiopathology involves the abnormal activity of at least one of the neuronal structures mentioned previously.

The evidence of an intricate neurocognitive network involved in time processing skills is a proof against the existence of a "mental clock" localized in a specific region of the brain. However, it makes it difficult to clarify if and what the majority (if not all) of mental disorders affected by timing deficits share at the psychophysiological level.

The goal of the current work is focusing on the contribution of interoception in the experience of time. Evidence in healthy humans (e.g., Pollatos et al., 2014b) shows that interoceptive awareness of the cardiac cycle is crucial to encode and reproduce durations of the range between 2 and 25 s (see also Meissner and Wittmann, 2011; Pollatos et al., 2014a). Moreover, we recently demonstrated that the manipulation of interoceptive signaling (i.e., appetite) affects the experience of time (Vicario et al., 2019). Finally, the insular cortex, a key neural region in decoding interoceptive signaling (Craig, 2009b), including the visceral emotion of disgust (see Vicario et al., 2017a,b for review) and appetite (Tataranni et al., 1999; Del Parigi et al., 2002), is implicated in the experience of time in healthy humans (e.g., Tregellas et al., 2006; Craig, 2009a; Wiener et al., 2010 for review). In keeping with this literature, we aim to explore the hypothesis that alterations in time processing, as reported in several clinical disorders, may be linked, at least in part, with dysfunctions of their interoceptive system, which depends on abnormal activity of insular cortex, as suggested by several works (e.g., Craig, 2009; Livneh et al., 2020). We have examined the available literature (giving priority to systematic reviews and/or meta-analysis) on timing deficits in clinical (i.e., neurological and psychiatric) disorders (schizophrenia, depression, anxiety and related disorders, eating disorders, attention-deficit hyperactivity disorder (ADHD), Tourette's syndrome (TS), autism, Parkinson's disease (PD), dystonia, essential tremor (ET), migraine) to explore the existence of dysfunctions of their interoceptive system at the behavioral and neural levels. Furthermore, we studied the existence of any specific relation between insular activation, which is involved in detecting/decoding interoceptive signaling (Craig, 2009b), and the subjective experience of time. In line with our aims, we only focused on research including supra-second durations, in keeping with the evidence of larger insula activation for this temporal range (Wittmann et al., 2010).

Schizophrenia

The literature on timing skills in schizophrenia is quite extensive (for recent contributions, see Capa et al., 2014; Giersch et al., 2015; Martin et al., 2018; Wilquin et al., 2018). In the meta-analysis by Thoenes and Oberfeld (2017), the authors documented a small and task-dependent tendency of patients to overestimate durations in time estimation/production. Timing dysfunctions can span from millisecond to second durations (Carroll et al., 2009). A similar result is reported in a subsequent meta-analysis (Ueda et al., 2018) in which a relation between positive symptoms of schizophrenia and temporal overestimation of supra-second durations was described (Ueda et al., 2018). Finally, alterations in time processing have been documented also via qualitative approaches such as by using inductive summarizing content analysis (Vogel D. H. V. et al., 2019), suggesting a link between disturbances in the experience of time and alterations in the constitution of the stream of consciousness (Vogel D. H. V. et al., 2019).

Schizophrenia is also affected by altered interoceptive function. Ardizzi et al. (2016) demonstrated a reduced interoceptive accuracy (measured via the heartbeat perception task) in this clinical population. Interestingly, the authors reported also a positive relationship between interoceptive accuracy and the positive symptomatology in this clinical population. Moreover, reduced insula activation was reported during the execution of a time discrimination task (Davalos et al., 2011). Overall, the literature suggests alterations of timing, and dysfunctions at the level of insula, and one study directly relates these two observations. Because positive symptoms positively correlate with interoceptive accuracy (Ardizzi et al., 2016) and time overestimation performance (Ueda et al., 2018) in schizophrenia, we speculate that their interoceptive dysfunction might potentially play a direct role in their timing response (i.e., temporal overestimation). Talking about the potential link between insular activation and the perceived duration, the study by Davalos et al. (2011) does not provide insight in this regard, as the data analysis provided in this study focused on the percentage of errors, with no information on the direction of errors (i.e., overestimation or underestimation error).

Depression

Depressed patients frequently report to perceive time as going by very slowly (Thönes and Oberfeld, 2015). As in the case of schizophrenia, also for depression further insights are

provided by qualitative research (Vogel et al., 2018) documenting disturbances in the experience of time, specifically difficulties with respect to influencing or changing the present, resulting in an impersonal and blocked future (Vogel et al., 2018). Bschor et al. (2004) provided one of the first studies on time sense in depression and documented a uniform time overestimation pattern of supra-second durations in patients affected by major depressive episode and manic episode in time judgment tasks. This result has been confirmed in a more recent work using a time reproduction task (Mioni et al., 2016). A meta-analysis on timing skills in depression (see Thönes and Oberfeld, 2015) did not provide conclusive results. However, this might be a result of the inclusion of studies on patients under medications that might have played some independent effect on timing performance.

Depression is also characterized by altered interoceptive functions. It was suggested that this clinical population is affected by alliesthesia for internal body signals (Paulus and Stein, 2010), as well as abnormal body perception (increased interoceptive awareness) and altered (increased) insula activation (see Sliz and Hayley, 2012 for a review).

Overall, the literature shows both an alteration of time processing and interoceptive dysfunction. Further studies are required to establish whether a link exists between these dysfunctions.

Anxiety and Related Disorders

Anxiety is another psychiatric disorder typically associated with abnormal time processing. Mioni et al. (2016) documented an under-reproduction of supra-second durations in this clinical population via time reproduction, which might indicate an overestimation in duration. Interestingly, an overestimation timing pattern was recently reported also in patients affected by post-traumatic stress disorder – PTSD (Vicario and Felmingham, 2018a).

Both anxiety and PTSD are also known to be associated with interoceptive dysfunctions (Martino G. et al., 2019). In anxiety, as well as in depression, symptoms of alliesthesia for internal body signals are present (Paulus and Stein, 2010). In PTSD, typical symptoms of interoceptive dysfunction include autonomic hypervigilance, depersonalization, and derealization (Glenn et al., 2017).

With regard to the insular cortex, higher activation in anxiety during affective tasks was reported (e.g., for a review see Paulus and Stein, 2010). The study by Simmons et al. (2009) reported a reduced insular activity in PTSD during the execution of affective tasks. However, a further work has reported higher activation in the right insula in this clinical population for affective stimuli (Bruce et al., 2012), which is also confirmed by earlier investigations (Shin et al., 1999).

Overall, the literature shows both an alteration of time processing and interoceptive dysfunction. Further studies are required to establish whether a link exists between these dysfunctions.

Eating Disorders

Patients with anorexia nervosa (AN) and hyperphagia are known for their deficit in perceiving interoceptive signaling. In AN, hunger insensitivity, food anxiety, and gastrointestinal complaints are reported (Khalsa et al., 2018), whereas hyperphagia symptoms include hypersensitivity to interoceptive signals of hunger and the inability to accurately detect interoceptive signals of satiety (Simmons and DeVille, 2017).

A dysfunction of the insular cortex is another hallmark in AN (Nunn et al., 2011) and might explain the high disgust sensitivity in this clinical population (Vicario, 2013a). A reduced BOLD response in the insula of recovered AN is reported in response to sucrose or water administration, compared with healthy controls (Wagner et al., 2008). In contrast, Scharmüller et al. (2012) found higher insular activation in response to food cues for obese people (for a review, see Frank et al., 2013).

In terms of time-keeping skills in eating disorders, two recent contributions document a temporal underestimation in AN (Vicario and Felmingham, 2018b) and a temporal overestimation in obesity (Vicario et al., 2019) for the estimation of supra-second durations.

Overall, the literature provides preliminary evidence of both an alteration of time processing and interoceptive dysfunction. Further work is required to establish whether a link exists between these dysfunctions.

Attention-Deficit Hyperactivity Disorder

The literature on timing deficits in ADHD is well consolidated (Toplak et al., 2006). Mullins et al. (2005) reported underestimation of supra-second durations in a time reproduction task (see also Pollak et al., 2009; Noreika et al., 2013, for a review). An fMRI study (Valera et al., 2010) found decreased insular activation during the execution of a sub-second timing – sensorimotor synchronization – task in ADHD. This pattern was confirmed in a meta-analysis of fMRI studies of timing in ADHD (Hart et al., 2012). Finally, a recent study by Wiersema and Godefroid (2018) did not reveal a significant difference between patients and healthy controls in the execution of interoceptive tasks, suggesting preserved interoceptive awareness in this clinical population. Overall, the research examined previously does not provide support to the hypothesis of a linking between interoception and timing deficits in ADHD.

Tourette's Syndrome

The research on timing skills in TS is still in its infancy. Studies of Vicario et al. (2010, 2016) confirmed a tendency of this clinical population to overestimate supra-second durations, in the absence of pharmacological treatment, in a time reproduction task (see also Martino D. et al., 2019; Vicario et al., 2020, for further contributions in the field of time processing). This response pattern correlated with tic severity (Vicario et al., 2010). Interestingly, fMRI research has shown an association between premonitory urges (tic severity) and the involvement of higher insular activation (for a review, see Worbe et al., 2015; Cavanna et al., 2017) in this clinical population. Pile et al. (2018) also confirmed reduced interoceptive accuracy, compared with healthy controls. Moreover, Ganos et al. (2015) found a positive correlation between premonitory urges (tic severity) and interoceptive awareness. Given the evidence that tic severity relates with time overestimation, interoceptive awareness, and

insular activation, we speculate that this timing pattern can be potentially linked with higher activity of the insular cortex in TS.

Overall, the literature shows both an alteration of time processing and interoceptive dysfunction. Further studies are required to establish whether a link exists between these dysfunctions.

Autism

Timing skills are abnormal in autism (e.g., for a review see Allman and Meck 2012; Falter et al., 2012). Temporal underestimation for supra-second durations has been observed in autism via time reproduction task (Martin et al., 2010). Moreover, by using an inductive content analysis, the results by Vogel D. et al. (2019) suggest that this disorder is affected by an interrupted time experience syndrome. A meta-analysis (Di Martino et al., 2009) documents right insula cortex hypoactivation in autism spectrum disorders during the execution of several affective/social tasks. In accordance, there is evidence of altered interoceptive functions in this clinical population (for a review, see Quattrocki and Friston, 2014; Garfinkel et al., 2016; Mulcahy et al., 2019). Overall, the research examined previously suggests that the time underestimation pattern in autism may be potentially linked with a lower activity of the insular cortex.

Parkinson's Disease

The literature on time processing in PD is wide (for a review, see Avanzino et al., 2016) and shows a relevance of dopaminergic degeneration/dysfunctions for this cognitive function (Lewis and Miall, 2006; Vicario, 2013b). The timing pattern most frequently reported in these patients in a tendency to underestimate supra-second durations in the absence of dopaminergic therapy (e.g., Koch et al., 2008) in a time reproduction task. Interestingly, the study by Harrington et al. (2011) in PD (L-Dopa off-state therapy) documented a reduction of insular activation during encoding of supra-second durations in these patients. Finally, evidence does exist for interoceptive alterations in PD. Ricciardi et al. (2016) documented lower interoceptive sensitivity (measured via the heartbeat perception task) in PD, as compared with controls. Overall, the literature shows both an alteration of time processing and interoceptive dysfunction. More research is required to establish whether a link exists between these dysfunctions.

Dystonia

The behavioral research in dystonia has documented timing deficits in cervical dystonia (Martino et al., 2015), as well as in writer's cramp (Avanzino et al., 2013). Both studies found an enhanced absolute value of timing error during the execution of a temporal expectation task, possibly linked with a cerebellar dysfunction (Avanzino et al., 2015; Martino et al., 2020), whereas no difference was reported with regard to the direction of timing performance (i.e., patients and controls underestimated longer durations in similar way). Ferrazzano et al. (2017) have recently documented reduced interoceptive sensitivity, as measured via the heartbeat detection task, in cervical dystonia. Moreover, there is evidence for reduced insular activity in this clinical population (Opavský et al., 2012). A direct link between time alteration and interoceptive dysfunction in this disease remains to be established.

Overall, the literature shows an alteration of time processing with no evidence of interoceptive dysfunction. More research is required to establish whether a link exists between these dysfunctions.

Essential Tremor

No published research has explored interoceptive sensitivity in ET so far. Nevertheless, a recent neuroimaging work has reported a decreased amplitude of low-frequency fluctuations (ALFFs) of blood oxygen level–dependent signals in correspondence of insular cortex (Wang et al., 2018). ALFF is an index used to characterize regional cerebral function (Wang et al., 2018). One study (Pedrosa et al., 2016) documents furthermore temporal underestimation in a reproduction task for both sub-second and supra-second durations in ET.

Overall, the literature shows an alteration of time processing with no evidence of interoceptive dysfunction. More research is required to establish whether a link exists between these dysfunctions.

Migraine

The literature on time processing in migraine offers some contribution. In a first investigation (Anagnostou and Mitsikostas, 2005), a timing overestimation of sub-second durations was documented in adults affected by migraine and depression. This pattern was replicated in a subsequent work (Zhang et al., 2012) in the absence of depression. More recently, a time overestimation response of supra-second durations was reported in a sample of adolescents affected by migraine (Vicario et al., 2014). In a recent review, Borsook et al. (2016) linked migraine with structural and functional alterations of insula. For example, Xue et al. (2012) reported increased insular activity during the resting-state fMRI (Xue et al., 2012). Moreover, migraine can be intended as an example of interoceptive disorder for the interoceptive nature of some associated symptoms (e.g., nausea, vomiting) (see Brennan and Pietrobon, 2018 for a review). Overall, the literature shows both an alteration of time processing and interoceptive dysfunction. More research is required to establish whether a link exists between these dysfunctions.

DISCUSSION

In this work, we explored if alterations of interoceptive functions and/or dysfunctions of the insular cortex can be found in clinical disorders affected by timing deficits. Overall, the examined research provides preliminary support to this hypothesis, although we found only three papers that directly relate timing and the insula.

With regard to the relevance of insular activation to predict the direction (overestimation vs. underestimation) of timing performance, the overall picture is not consistent. In the majority of the examined clinical disorders, the literature

shows, in independent contributions, time underestimation and reduced insula activation (i.e., PD, ET, autism, ADHD), and time overestimation and increased insula activation (i.e., TS, schizophrenia, depression, anxiety, and migraine). Interestingly, the latter timing pattern is in line with the study of Dirnberger et al. (2012) in healthy humans, documenting greater activation of the insula when time is overestimated. Moreover, this latter pattern might be associated with PTSD, if we focus on evidence of a larger insula activation.

In one third of the examined clinical disorders, the literature shows, again in independent contributions, time overestimation and reduced insula activation (i.e., hyperphagia) or time underestimation and increased insula activation (i.e., anxiety and AN). In dystonia, the results are not conclusive.

The role of insula on time processing seems to be selectively related with specific timing tasks, a specific stage of time processing and a specific duration range (i.e., supra-second duration) (e.g., the study of Wittmann et al., 2010 shows higher insula activation in the encoding stage of supra-second durations during a time reproduction). This suggests that the ideal task to test the relevance of interoceptive/insular cortex function on timing skills of the examined clinical populations should include these features. In keeping with these premises, if we focus our analysis on clinical populations (i.e., TS, migraine, ET, PD, autism, ADHD, depression, anxiety) tested via time reproduction of supra-second durations, the link between insula activity and the direction of the timing response appears consistent in all cases. A match (of independent reports) between increased insular activity and time overestimation is reported in migraine, TS, depression, and anxiety; vice versa, a match between decreased insular activity and time underestimation is reported in ET, PD, autism, and ADHD.

Limitations, which need to be addressed in future research, include various aspects. The current work does not allow providing a direct demonstration that timing performance in the examined clinical populations is linked with their interoceptive alterations as, in most cases, the examined literature has not directly explored this issue. Therefore, the analysis provided in our work should be taken with caution and considered as a starting point for a more systematic investigation of the topic addressed in our article. Furthermore, the number of neuroimaging investigations exploring timing skills in clinical populations is low: neuroimaging was included only in three clinical populations, and none of these three studies included a supra-second time reproduction task. Another limitation is the involvement of heterogeneous clinical populations with regard to pharmacological treatment. This might have contributed to inconsistent results, as several of the examined mental disorders are treated with dopaminergic and/or serotonergic drugs, which are known to influence temporal performance (Rammsayer, 1993). Finally, the heterogeneity of tasks/procedures adopted to test timing skills in their clinical populations should be taken into account.

The adoption of time processing protocols more directly related with the activity of insula and/or interoceptive functions (e.g., judging the timing of own heartbeats – Critchley et al., 2004), in combination with neuroimaging investigations and measures of interoceptive sensitivity, will allow to provide a direct contribution to the current hypothesis and, therefore, address the limits of our analysis, which are bounded with the limits of the current state of the art.

In conclusion, our work provides preliminary evidence in support of the hypothesis that insular cortex alterations, which probably play a main role in interoceptive dysfunctions of the examined clinical disorders, may contribute to explain timing deficits. Our results also provide preliminary evidence that the insula activity predicts the direction (over/underestimation) of the experience of time, when measured via supra-second time reproduction tasks. The exploration of the connection between insula activity, interoceptive dysfunctions, and timing alterations is a timely topic as it would contribute to expand the current knowledge/debate about how the gut–brain interaction influences cognitive and affective processes.

AUTHOR CONTRIBUTIONS

CV made significant contribution to the design of the review, the drafting, and revision of the manuscript. MN gave a significant contribution to the drafting and the revision of the manuscript. MS provided substantial contribution in the revision of the manuscript. LA provided substantial contribution in the drafting and revision of the manuscript. GM critically revised the manuscript and gave the final approval of the manuscript to be submitted. All authors contributed to the article and approved the submitted version.

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