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PSYCHOLOGICAL FACTORS AS DETERMINANTS OF MEDICAL CONDITIONS, VOLUME II

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Editorial: Psychological Factors as Determinants of Medical Conditions, Volume II

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Editorial on the Research Topic

Psychological Factors as Determinants of Medical Conditions, Volume II

Life expectancy is increasing world-wide, thus age-related diseases are becoming a major health concern. Chronic diseases and related outcomes, such as osteoporosis and associated fractures, diabetes, endocrine, and cardiovascular disease, may seriously impact people's quality of life and their perceived quality of life (Guicciardi, 2017; Marchetti et al., 2017; Catalano et al., 2020; Vita et al., 2020; Di Bari et al., 2021; Martino et al., 2021a,b,c). This impact may, in turn, lead to psychopathological consequences (Di Giuseppe et al., 2020a; Giusti et al., 2021). Indeed, psychopathological symptoms frequently occur in tandem with chronic medical conditions and can even predict, and impact, mortality independently of a wide range of potential confounders (Kiecolt-Glaser et al., 2002; Lapolla et al., 2012; Kelly et al., 2019).

Moreover, psychological aspects may also drive individual behavior, including adherence to medical advice, deeply conditioning the management of chronic diseases (Marchini et al., 2020, 2021a,b). Anxiety and depression, emotional distress (e.g., alexithymia, abnormal disgust processing), body integrity identity disorders, cognitive deficits, lead to a variety of functional somatic disorders and affect a patient's attitude to treatment, which can impact their perceived quality of life (Vicario, 2013; Craparo et al., 2016; Di Giuseppe et al., 2019; Conversano et al., 2020; Martino et al., 2020; Barchetta et al., 2021; Gangemi et al., 2021; La Rosa et al., 2021; Liotta et al., 2021; Vicario et al., 2021; Martino et al.). Therefore, overturning the usual causal direction body-mind, evidence exists regarding the key role of psychopathological factors in the history of chronic illness (Castelnuovo, 2010; Castelnuovo et al., 2015; Conversano, 2019; Martino et al., 2019; Caputo, 2020; Vicario et al., 2020b). A strict evaluation of the psychological variables could contribute to a better understanding of the individual condition and possibly predict the risk of the onset of new medical diseases or complications (Salehinejad et al., 2020; Lucifora et al., 2021; Sardella et al., 2021). This could suggest 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 (Vicario and Nitsche, 2013; Di Giuseppe et al., 2020b,c).

Following the previous Research Topic on Psychological Factors as Determinants of Medical Conditions (Martino et al., 2019), in this second volume, we aim to update the latest developments including interdisciplinary and multidisciplinary contributions in order to understand the interrelations among psychopathological aspects, somatic symptoms, and medical outcomes.

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Our collection includes 17 articles—four opinion articles, five review studies, and eight research studies—which address several aspects of body-psyche integration from a theoretical, research and intervention perspective. Nine articles focused on clinical samples, with specific regard to developmental psychopathologies (Di Giuseppe et al.; Sorrenti and Filippello), neurological disorders (Kelly et al.), learning disabilities (Cataudella et al.), personality disorders (Eikeseth et al.; Williams et al.), and chronic and medical conditions (Conversano and Di Giuseppe; Guicciardi et al., Martino et al.). Whereas, eight articles dealt with general populations in order to examine the role of personality characteristics or dispositions (Conversano et al.; Conversano et al.; Merlo et al.; Rymarczyk et al.) and some variables connected with emotion processing (Conversano; Gaggero et al.; Di Giuseppe et al.; Di Giuseppe et al.). Overall, this collection contributes to deepening the interrelations between physical and mental health and well-being, highlighting the need to summarize the existing research knowledge (Cataudella et al.; Conversano et al.; Gaggero et al.; Kelly et al.; Martino et al.), provide new empirical evidence (Conversano et al.; Di Giuseppe et al.; Guicciardi et al.; Merlo et al., Williams et al.), develop and validate measurement tools (Di Giuseppe et al.; Eikeseth et al.; Rymarczyk et al.), and discuss the advances in clinical treatments and approaches (Conversano; Conversano and Di Giuseppe; Di Giuseppe et al.; Sorrenti and Filippello).

We hope that the articles here presented may provide interesting insights and help researchers and practitioners grasping the complexity of human mind and embracing a health promotion perspective, attentive to improving individuals' quality of life and adjustment processes at a physical, mental, and social level (Tomai et al., 2019; Vicario et al., 2020a; Conversano et al.; Conversano et al.).

It has been very pleasant and exciting for us to continue dealing with such issues and be newly involved in this Research Topic. In this regard, our thanks go out to all of them who made it possible, specifically Authors for their endeavors and interesting contributions, Reviewers for their competences and the time devoted, and the entire Frontiers Editorial and Developmental Staff for their patience and precious continued assistance.

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AC and GM wrote the first draft of the manuscript and revised it critically. CMV and VC provided opinions on it. All authors read and approved the submitted version.

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SYSTEMATIC REVIEW
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Mindfulness, Compassion, and Self-Compassion Among Health Care Professionals: What's New? A Systematic Review

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Health care professionals (HCPs) are a population at risk for high levels of burnout and compassion fatigue. The aim of the present systematic review was to give an overview on recent literature about mindfulness and compassion characteristics of HCPs, while exploring the effectiveness of techniques, involving the two aspects, such as MBSR or mindfulness intervention and compassion fatigue-related programs. A search of databases, including PubMed and PsycINFO, was conducted following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines and the methodological quality for this systematic review was appraised using AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews-2). The number of articles that met the inclusion criteria was 58 (4 RCTs, 24 studies with pre-post measurements, 12 cross-sectional studies, 11 cohort studies and 7 qualitative studies). MBSR intervention was effective at improving, and maintaining, mindfulness and self-compassion levels and to improve burnout, depression, anxiety, stress. The most frequently employed interventional strategies were mindfulness-related trainings that were effective at improving mindfulness and self-compassion, but not compassion fatigue, levels. Compassion-related interventions have been shown to improve self-compassion, mindfulness and interpersonal conflict levels. Mindfulness was effective at improving negative affect and compassion fatigue, while compassion satisfaction may be related to cultivation of positive affect. This systematic review summarized the evidence regarding mindfulness- and compassion-related qualities of HCPs as well as potential effects of MBSR, mindfulness-related and compassion-related interventions on professionals' psychological variables like mindfulness, self-compassion and quality of life. Combining structured mindfulness and compassion cultivation trainings may enhance the effects of interventions, limit the variability of intervention protocols and improve data comparability of future research.

Keywords: mindfulness, compassion, self-compassion, empathy, health care, health care professional

INTRODUCTION

Mindfulness has been defined as the awareness that arises by intentionally paying attention, in the present moment and in a non-judgmental way, to the flow of experience (Kabat-Zinn, 2003). Mindfulness is a theoretical instance that finds its implementation in a set of meditation and psycho educational exercises aimed at understanding certain fundamental themes such as stress, attachment and dependence on internal and external content and therefore the importance of subjective observation of thoughts, emotions, and physical sensations (Kabat-Zinn, 2009; Rosa et al., 2019). Mindfulness propensity is known as facilitators of well-being and adaptation for healthcare professionals, together with high adaptive defense mechanisms (Catalano et al., 2019; Di Giuseppe et al., 2019a, 2020a,c; Martino et al., 2020a). Moreover, mindfulness interventions proved to be very helpful in reducing the psychopathological symptomatology of chronic conditions (Bonadonna, 2003; Catalano et al., 2017; Poli et al., 2017, 2019; Conversano and Marchi, 2018; Marchini et al., 2018; Conversano, 2019; Di Giuseppe et al., 2019b, 2020b; Martino et al., 2019a,b, 2020b; Merlo, 2019; Conversano et al., 2020a; Lenzo et al., 2020; Poli et al., 2020).

The most widespread protocol used both in the clinical and in the normal context is represented by a group-based intervention named Mindfulness-Based Stress Reduction (MBSR). It is a protocol characterized by the teaching of formal and informal meditation practices, yoga exercises and the sharing of group experiences (Kabat-Zinn, 2009). The aim of MBSR is to improve mindfulness ability in participants, helping them to integrate their mind and body activity in a non-judgmental way. Starting from the MBSR program, in the following years, many protocols based on it have been developed for research purposes, integrating various aspects of psychological and behavioral sciences (Shonin et al., 2013).

A plethora of research show that mindfulness-based interventions (MBIs) determine significant benefits both in clinical and non-clinical samples. On the one hand, MBIs would seem to increase awareness levels, strategies to cope with stressful situations and emotion management; on the other hand, they seem to reduce levels of perceived stress, anxiety, and depressive symptoms (Brown and Ryan, 2003; Cahn and Polich, 2006; Chiesa and Serretti, 2011). Generally, MBIs have shown a significant correlation with positive improvements in the following areas: attention, cognition, behavior and physiological processes which probably influence the functioning of the individual and their quality of life (Veltri et al., 2012; Jha et al., 2019; Marchi et al., 2019; Marazziti et al., 2020).

Tang et al. (2018), in their review, have emphasized how mindfulness acts mainly on three systems, such as attentional control, emotional regulation and self-awareness. The authors also highlighted that mindfulness practice can produce changes in both density and volume in gray matter, finding the following areas involved in mindfulness meditation: various prefrontal regions, anterior cingulate cortex, medial prefrontal cortex, striatum, amygdala, insula, posterior cingulate cortex and precuneus. Furthermore, the central effect that mindfulness practice plays on stress axes, together with plastic brain aspects elicited by practice and positive regulation of the immune system activity, may be conceptualized as the outcome of brain modification through mindfulness. Furthermore, a recent review highlights how meditation can elicit a meta-functioning of awareness in those who practice, allowing an increased mind/body regulation system (Giannandrea et al., 2019).

In particular, mindfulness training seems to increase three qualities of attention: (1) Attentional stability, meant to focus sustained attention without wandering. It is estimated that the human mind gets distracted for about half of the waking hours; mindfulness, both state and trait, is associated with a reduction in mental digressions, bringing the person back to focus on the present (Killingsworth and Gilbert, 2010; Smallwood and Schooler, 2015); (2) voluntary control of attention or selective attention, the ability to direct attention to a specific topic rather than another in an appropriate and voluntary manner (Wadlinger and Isaacowitz, 2011); (3) efficiency of attention, or an economic use of cognitive resources, involving less expenditure of cognitive activities for an attention performance on a specific task. Since mindfulness is based on the ability to control and orientate attention, it was also associated with an improvement in efficiency (Cahn and Polich, 2009). Regarding neural networks (Menon and Uddin, 2010; Menon, 2011; Piccinni et al., 2012), several studies are investigating the effects of mindfulness on the default mode network (DMN), the neural processes underlying spontaneous thoughts and wandering mind. In psychopathology, the DMN is often found to be hyperactivated and hyperconnected (Whitfield-Gabrieli and Ford, 2012). Research investigating expert mindfulness meditators engaging in simple breathing practice showed that activity in brain regions associated with the DMN was present during mind wandering, and in salience network (SN) areas during awareness of mind wandering, while regions of the executive network were active during shifting and sustained attention (Hasenkamp et al., 2012; Scheibner et al., 2017; Orrù et al., 2020a,b), and the effects were modulated by lifetime meditation experience (Brewer et al., 2011; Hasenkamp and Barsalou, 2012). Furthermore, research has shown that mindfulness training can lead to changes in the SN that regulates the switching between DMN and central executive network. Following mindfulness meditation, but not relaxation training, central regions of the SN, the left anterior cingulate cortex (ACC) and insula, showed improved cerebral blood flow (Tang et al., 2015). Similarly, loving-kindness meditators showed a deactivation of main nodes of the DMN (Brewer et al., 2011) and, after few weeks of compassion training, novice meditators showed significant reductions of mind wandering (Jazaieri et al., 2014). Taken together, these results suggest that though the focus of compassion meditation does not involve regulating attentional processes on a specific object, compassion training does have an impact on attentional processes involved in DMN.

Mental training following a mindfulness-based program seems to increase cognitive abilities both as cognitive capacity and as cognitive flexibility. The first includes working memory and fluid intelligence, the second supports the adaptation of an individual using new answers and strategies. Mindfulness training is associated with an increased working memory

capacity, cognitive flexibility and benefits on fluid intelligence (Roeser et al., 2013; Ruocco and Direkoglu, 2013; Jha et al., 2019). It also promotes creative thinking and problem-solving skills (Colzato et al., 2012; Ostafin and Kassman, 2012; Raffone and Srinivasan, 2017).

Moreover, through mindfulness programs, participants may notice a different emotional regulation and functioning style; studies on the subject shows that mindfulness influences emotions both in terms of psychological reaction to emotion and tone or emotional value (positive or negative emotions). The increase in emotional regulation, or the set of processes and behavioral and cognitive strategies through which individuals influence their own emotional states following a mindfulness treatment, is related to an enhancement cognitive control mechanisms that refer to areas of the cortex prefrontal, such as the dorsolateral prefrontal cortex and prefrontal cortex ventromedial, and the anterior cingulate cortex, which act on the areas of the limbic system, used to process affective stimuli, such as the amygdala and the hippocampus (Chambers et al., 2009; Dell'Osso et al., 2012; Hölzel et al., 2013).

Furthermore, researchers found mindfulness training associated with a lower reactivity to stressful situations and negative emotional stimuli as it would increase the individual's ability to judge the situation more objectively and more emotionally of a positive value compared to those of a negative type (Farb et al., 2007; Hülsheger et al., 2013). Mindfulness exercises are related to a lower activation of the hypothalamic-pituitary-adrenal axis and cortisol secretion, influencing the stress response and its regulation, leading to a greater brain neuroplasticity and slowing the brain aging process (Brewer et al., 2011; Hölzel et al., 2013; McEwen and Morrison, 2013; Creswell and Lindsay, 2014; Fox et al., 2014; Luders et al., 2015).

More recently, some authors observed the importance of the ethical framework around mindfulness experiences. In particular, the authors postulate a theory which highlights the interrelation between the ethical beliefs of the individual and his relationship to the environment; cultivating internal and external awareness seems to arouse a process of ethics embodied in moral cognition. In fact, the changes reported by literature in MBI participants involve a meta-awareness and a different perspective of the self, probably influencing the processing of morally-relevant situations and stimuli thus encouraging moral action (Sevinc and Lazar, 2019). However, HCPs often suffer from psychological distress and therefore experience a varied spectrum of symptoms related to this condition. Specifically, a situation of psychological stress is able to elicit sleep disturbances (Palagini et al., 2016), cognitive problems, post-traumatic stress disorder (Marazziti et al., 2008; Mula et al., 2008) and also a burnout condition (Carmassi et al., 2016, 2017b, 2018; Moss, 2017; Conversano et al., 2020b).

Three types of meditation are typically included among "mindfulness meditations" in the West, namely focused attention, open monitoring (both attentional practices), and loving-kindness and compassion (both constructive practices) (Salzberg, 2011; Germer and Siegel, 2014). Focused attention entails bringing your attention back, again and again, to the breath or another focal object; open monitoring (or choiceless awareness) involves noticing what is most salient and alive in your field of awareness, moment-to-moment; loving-kindness meditation entails intentionally cultivating happiness while compassion meditation is about cultivating goodwill in the face of suffering (Germer and Siegel, 2014). While attentional meditation practices (focused attention and open monitoring) require focusing on a focal object or on a component part of the self, like perception, emotion, cognition or intention, loving-kindness, and compassion meditation require the self as the object of practice (Olendzki, 2013; Germer and Siegel, 2014; Dahl et al., 2015).

In particular, compassion is defined by Paul Gilbert, and the Buddhist monk Choden, as a sensitivity to suffering in self and others with a commitment to try to alleviate and prevent it (Gilbert, 2018), while self-compassion is defined by Kristin Neff as "being open to and moved by one's own suffering, experiencing feelings of caring and kindness toward oneself, taking an understanding, non-judgmental attitude toward one's inadequacies and failures, and recognizing that one's experience is part of the common human experience" (Neff, 2003). Recent brain imaging research supports the notion of evaluating compassion as more emotionally engaging than mindfulness. Compassion practice was found to activate regions of the positive affect system, such as the medial orbitofrontal cortex, nucleus accumbens and the ventral striatum (Klimecki et al., 2013, 2014; Engen and Singer, 2015). Specifically, Engen and Singer (2015) compared compassion meditation in response to cognitive reappraisal and showed that, in response to empathic distress, compassion meditation activated brain systems associated to positive emotion, while cognitive reappraisal recruited cognitive control regions and reduced activation of the negative affect system regions. Research also pointed out that mindfulness practitioners show reduced activation and structural changes of the amygdala (Hölzel et al., 2013; Taren et al., 2013, 2015). Overall, these results suggest that beneficial effects of mindfulness and compassion practices may act through different mechanisms: mindfulness reduces negative affect system's activity while compassion increases activity of positive emotion brain systems.

Interestingly, it has been shown that transcutaneous vagus nerve stimulation is able to modulate DMN in major depressive disorder (Fang et al., 2016) and that increased vagal activity was associated with higher compassion levels (Stellar et al., 2015). It has been shown that adopting a true compassionate disposition when viewing pictures of people suffering activated the mesolimbic dopamine pathway (ventral tegmental area and the ventral striatum) implicated in reward and bond formation (Kim et al., 2009). More recently, research showed that the septal nuclei, another area that is relevant for reward and prosocial motivation, was the unique region that was typically activated across empathy for pain, anxiety and happiness. Septal activation in course of these empathic experiences was predictive of helping (Morelli et al., 2014). Remarkably, it was recently shown that optogenetic activation of gut-innervating vagal sensory neurons, namely the dorsolateral parabrachial-nigral projections, mimicked the rewarding effects of right vagus excitation and identifies dorsolateral parabrachial region as the mandatory

retransmission region linking the right vagal sensory ganglion to dopamine cells in substantia nigra (Han et al., 2018).

Interestingly, studies investigating compassion are consistent with those emerging from research on the neurobiology of the parental brain. It has long been observed in animal models that both the septal nuclei and the mesolimbic dopamine pathway are implicated in motivating proactive offspring nurture (Champagne et al., 2001). Specifically, ventral tegmental area dopaminergic neurons projecting to the nucleus accumbens motivate caregiving (Numan and Stolzenberg, 2009). Recent neuroimaging evidence suggests that this system may support human parental motivation to nurture their toddlers (Mascaro et al., 2013; Rilling, 2013), increasing the probability that this system underpins the motivational quality of compassion (Preston and Hofelich, 2012) and that compassion coopts the systems that evolved for maternal attachment (Preston and de Waal, 2001).

While it is very important that health care professionals (HCPs) continue to work with empathy and compassion, since compassionate motivation may impinge on the same circuits of maternal attachment, there may be a cost to this work that is also closely related to past maternal experience of HCPs. The concept of compassion fatigue first emerged with the work of Charles Figley, who defined it as "the formal caregiver's reduced capacity or interest in being empathic or 'bearing the suffering of clients' and is 'the natural consequent behaviors and emotions resulting from knowing about a traumatizing event experienced or suffered by a person'" (Figley, 1995, 2002; Di Giuseppe et al., 2018). Compassion fatigue can be defined as secondary traumatic stress resulting from knowing about a traumatizing event experienced by a significant traumatized or suffering person (Figley, 1995, 2002). Prevalence of compassion fatigue has been reported to range as 7.3 to 40%, while the prevalence of secondary traumatic stress has been reported to range from 0 to 38.5% in intensive care units (Mol et al., 2015). Compassion fatigue often is assumed to accompany another version of fatigue known as burnout. Specifically, hard workloads, lack of recognition for achievements, and social disconnection from the team can result in burnout, suggesting the need to reduce the hours supporting the patient for formal (Amankwaa, 2017; Mattioli et al., 2018; Castellanos et al., 2019; Allday et al., 2020) as well informal (Peetoom et al., 2016; Lethin et al., 2017; Hampton and Newcomb, 2018; Wood et al., 2018) caregivers. However, compassion for another may originate from compassion for self. Gustin and Wagner (2013) found that developing a compassionate self and the aptitude to be sensitive, non-judgmental and regardful toward oneself promotes a compassionate approach toward others. Thus, developing self-compassion may be an important hindering factor of compassion fatigue and promotion of compassionate care (Neff, 2009) and mindfulness and self-compassion may be appropriate target variables to alleviate work-related stress and promote compassionate caregiving in HCPs.

The aim of the present systematic review was to give an overview on recent literature about mindfulness, compassion and self-compassion characteristics and to investigate the effectiveness of techniques involving MBSR or mindfulness-related interventions and/or compassion- or self-compassion-related programs, to identify the interventions with the best level of evidence available to prevent, or mitigate, HCPs' burnout and to improve their levels of mindfulness and/or compassion- or self-compassion, emotional regulation, quality of life and well-being.

METHODS

This review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (Liberati et al., 2009; Moher et al., 2009).

Search Strategy

Searches were conducted using PubMed and PsycInfo databases. Searches were conducted from January 2004 to May 2020 and were limited to English and Italian language papers. PubMed and PsycInfo databases were searched by three independent reviewers (CC, RC, and AP) using a combination of the keywords "Health Personnel," "Mindfulness," "Self-Compassion," "MBSR," using the Boolean operators AND/OR.

Study Selection

The selection of studies is shown in **Figure 1**, using the PRISMA flow diagram (Liberati et al., 2009; Moher et al., 2009). The search identified 603 articles, which were screened for eligibility. We removed duplicates and corrigenda (383) and then selected the articles which presented at least one or both mindfulness and compassion component and a healthcare unit/personnel/professional in title or abstract and removed those considered ineligible. Ninety-four full-text articles were retrieved and read in full by three reviewers (CC, RC, and AP) and divided by type and study design and, finally, we excluded descriptive, single case and post intervention studies and reviews. Qualitative studies are included. Studies that did not report measures of mindfulness and self-compassion were excluded. Overall, while the authors were independently reading the articles, 38 articles were excluded from the results due to (a) not in accordance with the main topic (b) study design not included (b) full text not available. A total of 58 studies were included in the review (**Table 1**).

Eligibility Criteria

All studies included in our review examined the effect of MBSR, MBIs (interventions including predominantly mindfulness elements; Spinelli et al., 2019); and compassion-based interventions (CBIs, interventions including predominantly compassion elements; Kirby, 2017); on mindfulness and self-compassion qualities of HCPs. Interventions using yoga, or other meditative practices, and MBIs that used the key therapeutic approaches, such as body scan meditations or acceptance or non-judgmental strategies, were included.

Data Extraction

At an earlier stage, titles and abstracts were screened for eligibility by one reviewer (CC) to characterize abstracts as highly relevant, potentially relevant, or not relevant. Full texts

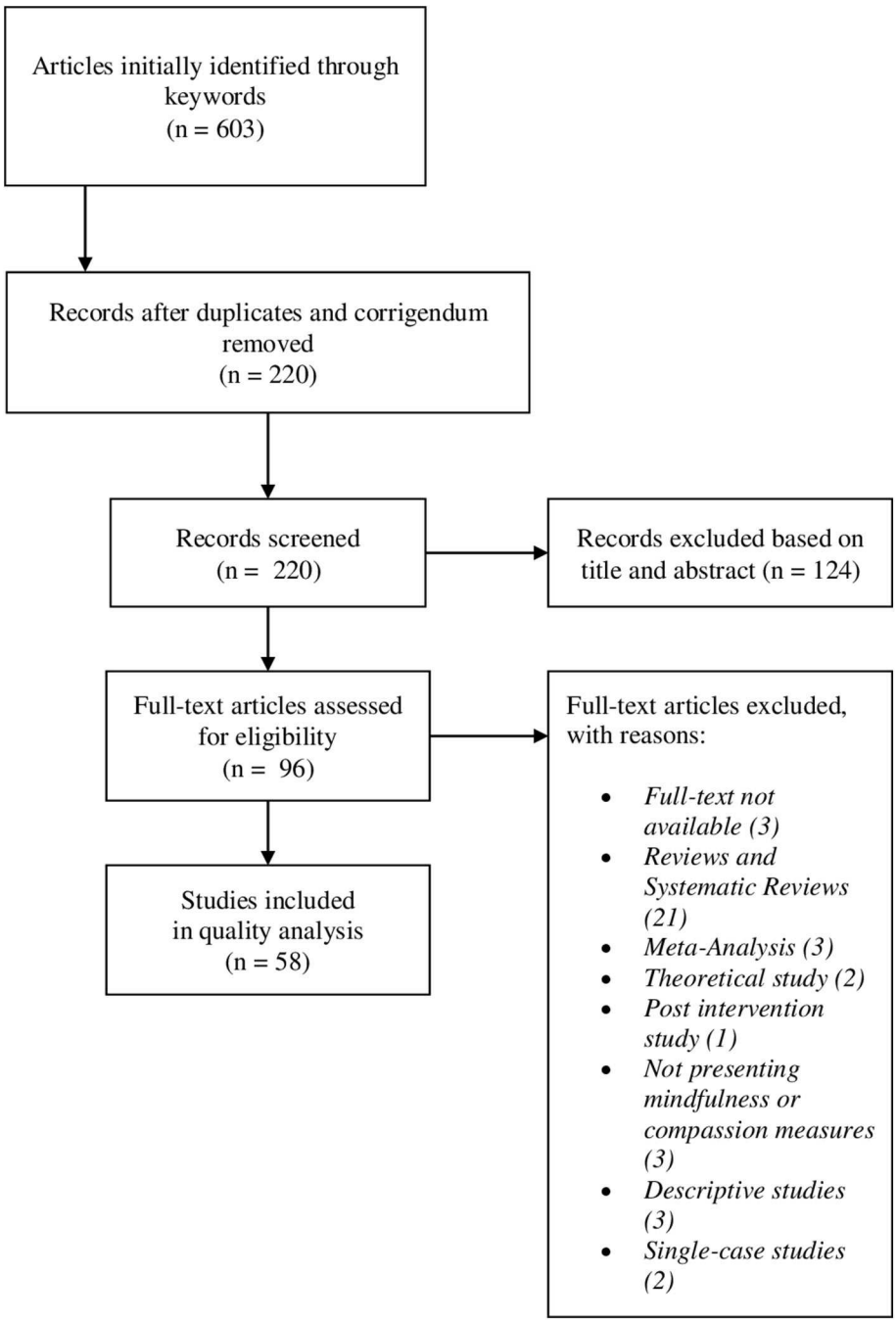

FIGURE 1 | PRISMA Flow chart for literature search and screening results.

were then accessed for all abstracts characterized as highly or potentially relevant and read in full by three reviewers (CC, RC, and AP) to determine whether they were eligible. Studies that were considered ambiguous, with respect to the inclusion criteria, were discussed, and consensus was reached for all articles included.

The following data was extracted from each eligible study report by RC and verified by CC, GO, AG, or AP: first author name, title, publication date, aim and design, key sample characteristics (including age, gender, and healthcare profession), type of intervention, comparison, main outcome measures, and results.

Quality Assessment

The appraisal of the methodological quality for this systematic review was based on AMSTAR-2 (A MeaSurement Tool to

TABLE 1 | Summary of the revised studies.

	Authors	Title	Year
1	Allie et al.	Bereavement overload and its effects on, and related coping mechanisms of health care providers and ward administrators at National District Hospital in Bloemfontein, Free State	2018
2	Al-Majid et al.	Assessing the degree of compassion satisfaction and compassion fatigue among critical care, oncology, and charge nurses	2018
3	Amutio et al.	Acceptability and effectiveness of a long-term educational intervention to reduce physicians' stress-related conditions	2015
4	Brady et al.	The impact of mindfulness meditation in promoting a culture of safety on an acute psychiatric unit	2012
5	Brooker et al.	Evaluation of an Occupational Mindfulness program for staff employed in the disability sector in Australia	2013
6	Brown et al.	Compassion fatigue and mindfulness: comparing mental health professionals and MSW student interns	2017
7	Cohen-Katz et al.	The effects of mindfulness-based stress reduction on nurse stress and burnout: a quantitative and qualitative study	2004
8	Copeland and Henry	The relationship between workplace violence, perceptions of safety, and Professional Quality of Life among emergency department staff members in a Level 1 Trauma Centre	2018
9	Dev et al.	Does self-compassion mitigate the relationship between burnout and barriers to compassion? A cross-sectional quantitative study of 799 nurses	2018
10	dos Santos et al.	Positive effects of a stress reduction program based on mindfulness meditation in Brazilian nursing professionals: qualitative and quantitative evaluation	2016
11	Duarte and Pinto-Gouveia	Mindfulness, self-compassion and psychological inflexibility mediate the Brady effects of a mindfulness-based intervention in a sample of oncology nurses	2017
12	Duggan and Julliard	Implementation of a mindfulness moment initiative for healthcare professionals: perceptions of facilitators	2018
13	Eliassen et al.	The effect of training in mindfulness and affect consciousness on the therapeutic environment for patients with psychoses: an explorative intervention study	2016
14	Erkorkmaz et al.	The relationship between burnout, self-esteem and professional life quality of nurses	2018
15	Farina et al.	Introducing mindfulness practices for self-care: outcomes of a brief education session	2018
16	Fernando et al.	Increasing compassion in medical decision-making: can a brief mindfulness intervention help?	2017
17	Gracia-Gracia and Oliván-Blázquez	Burnout and mindfulness self-compassion in nurses of intensive care units: cross-sectional study	2017
18	Horner et al.	A pilot study to evaluate mindfulness as a strategy to improve inpatient nurse and patient experiences	2014
19	Hunter et al.	Being there and reconnecting: midwives' perceptions of the impact of Mindfulness training on their practice	2018
20	Ireland et al.	A randomized controlled trial of mindfulness to reduce stress and burnout among intern practitioners	2017
21	Kemper	Brief online mindfulness training: immediate impact	2017
22	Kemper and Rao	Brief online focused attention meditation training: immediate impact	2017
23	Kemper et al.	What is the impact of online training in mind-body skills?	2015
24	Kemper and Khirallah	Acute effects of online mind-body skills training on resilience, mindfulness, and empathy	2015
25	Klatt et al.	A pragmatic introduction of mindfulness in a continuing education setting: exploring personal experience, bridging to professional practice	2017
26	Lamothe et al.	Developing professional caregivers' empathy and emotional competencies through mindfulness-based stress reduction (MBSR): results of two proof-of-concept studies	2018
27	Luthar et al.	Fostering resilience among mothers under stress: "Authentic Connections Groups" for medical professionals	2017
28	Lyddy et al.	Transfer of mindfulness training to the work setting: a qualitative study in a health care system	2016
29	McPherson et al.	Distress in working on dementia wards—a threat to compassionate care: a grounded theory study	2016
30	Montero-Marin et al.	Burnout subtypes and absence of self-compassion in primary healthcare professionals: a cross-sectional study	2016
31	Morrison Wylde et al.	Mindfulness for novice pediatric nurses: smartphone application vs. traditional intervention	2017
32	Ofei-Dodoo et al.	Impact of a mindfulness-based, workplace group yoga intervention on burnout, self-care, and compassion in health care professionals: a pilot study	2020

(Continued)

TABLE 1 | Continued

	Authors	Title	Year
33	Olson et al.	What factors promote resilience and protect against burnout in first-year pediatric and medicine-pediatric residents?	2015
34	O'Mahony et al.	A Multimodal Mindfulness training to address mental health symptoms in providers who care for and interact with children in relation to end-of-life care	2016
35	Orellana-Rios et al.	Mindfulness and compassion-oriented practices at work reduce distress and enhance self-care of palliative care teams: a mixed-method evaluation of an "on the job" program	2017
36	Pakenham et al.	Effects of Acceptance and Commitment Therapy (ACT) training on clinical psychology trainee stress, therapist skills and attributes, and ACT processes	2015
37	Pfaff et al.	Reducing the "cost of caring" in cancer care: evaluation of a pilot interprofessional compassion fatigue resiliency programme	2017
38	Pflugeisen et al.	Brief video-module administered mindfulness program for physicians: a pilot study	2016
39	Platt et al.	Fostering resilience with GPs: a workshop approach	2015
40	Powell et al.	Work-Life BALANCE: How Some Case Managers Do It!	2018
41	Raab et al.	Mindfulness-based stress reduction and self-compassion among mental healthcare professionals: a pilot study	2015
42	Riley et al.	Improving physical and mental health in frontline mental health care providers: yoga-based stress management vs. cognitive behavioral stress management	2017
43	Ripp et al.	Well-being in graduate medical education: a call for action	2017
44	Roney and Acri	The cost of caring: an exploration of compassion fatigue, compassion satisfaction, and job satisfaction in pediatric nurses	2018
45	Sanso et al.	Evaluation of a mindfulness intervention in palliative care teams [Spanish]	2018
46	Scarlet et al.	The effects of Compassion Cultivation Training (CCT) on health-care workers	2017
47	Shapiro et al.	Mindfulness-based stress reduction for health care professionals: results from a randomized trial	2005
48	Silver et al.	Mindfulness among genetic counselors is associated with increased empathy and work engagement and decreased burnout and compassion fatigue	2018
49	Steinberg et al.	Feasibility of a mindfulness-based intervention for surgical intensive care unit personnel	2016
50	Suyi et al.	Effectiveness of mindfulness intervention in reducing stress and burnout for mental health professionals in Singapore	2017
51	Taylor et al.	A mindfulness intervention for residents: relevance for pediatricians	2016
52	Valley and Stallones	A thematic analysis of health care workers' adoption of mindfulness practices	2018
53	Valley and Stallones	Effect of mindfulness-based stress reduction training on health care worker safety: a randomized waitlist controlled trial	2017
54	Verweij et al.	Mindfulness-based stress reduction for GPs: results of a controlled mixed methods pilot study in Dutch primary care	2016
55	Wacker and Dziobek	Preventing empathic distress and social stressors at work through non-violent communication training: a field study with health professionals	2018
56	Wahl et al.	Implementing a Peer Support Network to Promote Compassion Without Fatigue	2018
57	Wen et al.	Encouraging mindfulness in medical house staff via smartphone app: a pilot study	2017
58	Wijdenes et al.	Assessing compassion fatigue risk among nurses in a large urban trauma center	2019

Assess systematic Reviews-2) (Shea et al., 2017) approach. It enables a more detailed assessment of systematic reviews that include randomized or non-randomized studies of healthcare interventions, or both. Two independent raters assessed each study (CC and RC), and seven discrepancies were found regarding AMSTAR-2 checklist coding. Then, a discussion took place to resolve divergences, consulting a third rater (AP), if necessary, until consensus was reached.

Analysis

After examination of included articles, meta-analysis was not considered suitable as there were insufficient studies with the required level of homogeneity regarding MBIs, CBIs, outcome measures, and the timing of these measures. Therefore, the findings are summarized using a narrative, but systematic, approach.

RESULTS

The included experimental studies showed several different types of design such as: randomized controlled trials (4), studies with pre-post measurements (24), cross-sectional studies (12), cohort studies (11), and qualitative studies (7).

Among the included articles, some of the experimental studies investigated the effectiveness of an intervention based on MBSR (Kabat-Zinn, 2009) or compassion-related interventions (Neff and Germer, 2013) in relation to psychological variables and factors related to quality of life in HCPs. Some studies compared

MBSR, mindfulness-related interventions, compassion-related interventions with untreated control groups, while other studies cross-sectionally probed mindfulness or compassion variables in the investigated sample, trying to find correlations with other professional variables such as burnout and empathy that did not undergo any kind of intervention. We highlight that some studies have concerned online interventions both in terms of their creation and impact on health outcomes.

Qualitative Studies

With regard to mindfulness interventions, Ripp et al. (2017) highlight its importance in the fight against burnout in graduate medical trainees together with "resilience training, stress and self-care management workshops, communication skills training, narrative medicine, reflection opportunities and peer support grounded in group discussions."

Hunter et al. (2018) conducted a qualitative study through an interpretative phenomenological analysis of semi-structured interviews. The measures were operated on midwives after a MBI, either at or outside workplace. Nine midwives selected to take part in the study, and the findings were divided in four superordinate themes: being challenged and committing, containing the self, reconnecting and moving forward with confidence. Results showed that, despite an initial and normal skepticism about mindfulness practice, those that committed to the concept of living in the present moment benefitted from an increased self-awareness of self which presumably leads to both an increase of positive workplace relationships and individualized and relation patient care.

The research trio of McPherson et al. (2016) conducted a study to explore the experiences of managing work pressures of staff caring for older adults with dementia through compassion and mindfulness skills. The interviewer used a constructivist grounded theory approach which is guided by participants themselves, finding two main types of work-related pressure (structural or interpersonal) and two different types of responses (helpful and unhelpful). In the helpful strategies, taking a moment, talking, reflecting, and processing were included, but did not reach a sufficient level to be considered practice. The authors also found some barriers to the full experience of the self-compassionate and mindful state, which leads to their suggestion of increasing structured mindfulness interventions in HCPs.

Platt et al. (2015) wrote a qualitative paper about a workshop which was planned for general practitioners, comprehending stress management sessions, art or puppetry and mindfulness sessions. This workshop's aim was to help the participants develop a better self-awareness when facing stress situations and identify different ways to manage the stress response. The 25 participants were interviewed during the workshop and 2 months after it (by an online survey), for feedback. Results showed that this kind of intervention was well-received, with immediate to medium-term impact on the individual.

Lyddy et al. (2016) explored how health professionals, which had previously followed a mindfulness-based course, and use and perceive mindfulness practice during their work. The measurement was carried out through a semi-structured guide with open-ended questions, also including questions about role and recent prototypical job experiences. Their results highlight that participants varied in the subsequent adoption of mindfulness exercises, often struggling with the formal meditation practice routine and using the informal practice models taught during the course. The authors suggested that mindfulness training in hospitals should include practice in the actual workplace to increase realism and integration of practice on a daily basis and practice in identifying the value of mindfulness at work through guided experimentations.

In their interesting work, Valley and Stallones (2018) also aimed at confirming the role of mindfulness interventions in the development of self-awareness, using the Health Belief Model (HBM) to help explain and predict the adoption of a variety of preventive and treatment health behaviors. In their research of what is needed to improve mindfulness interventions in health care workers, they found that adapting the course timing and materials to meet the HCPs' schedule and a didactic material which explains the evidence of those interventions should be provided to the participant in order to increase the participation and adherence to the courses.

Looking at the issue from the opposite point of view, Powell et al. (2018) have raised the question of what makes some health professionals more protected from the risk of burnout than others. In her work, she asked through a convenience survey, administered to some multidisciplinary staff members about their activities outside work which "provides a balance to the daily triumphs and challenges of their work–life in case management" and if the activity "enhance their life at work" and how. Although only 32 of those staff members replied to the survey, we can highlight that the findings included meditation, mindfulness, exercise, nature and animals, family and friends as activities indicated by the participants which could lead to some sort of balance during work.

Randomized Controlled Trials

Shapiro et al. (2005) conducted a RCT on the effectiveness of MBSR training in a population of HCPs, directly involved in clinical work, in particular measuring the stress and distress response and job burnout. For the MBSR participants, lower stress level and higher self-compassion was reported, with a reduction of job burnout. Unfortunately, these results didn't differ significantly from the control group, contrary to their qualitative data.

Amutio et al. (2015) tested both acceptability and effectiveness of an MBSR with a maintenance phase (8 week traditional intervention plus 10 month of maintenance) with the aim to alleviate work-stress related symptoms such as burnout and blood pressure levels. Their findings showed decreased burnout (especially emotional exhaustion subscale), blood pressure and heart rate, which were still decreasing after 10 months from the MBSR programme. Similarly, Ireland et al. (2017) tested the effectiveness of a mixed mindfulness intervention in reducing stress and burnout among doctors assigned to an emergency department rotation programme. Also, their findings suggested a decreased stress and burnout of the participants, to a greater extend that an assigned extra break hour for 10 weeks.

Finally, Valley and Stallones (2017) RCT study examined the impact of mindfulness training on occupational safety of hospital HCPs, through an MBSR intervention, measuring safety outcomes (compliance and participation). Their results indicated that mindfulness was able to stably decrease workplace cognitive failures while increasing the following of safety rules, collaboration, and safety compliance behaviors. The authors highlight the importance of these findings which could impact the degree of occupational injuries.

Cross-Sectional Studies

Understanding the Link Between Compassion Fatigue and Compassion Satisfaction, Bereavement Overload, Burnout, and Violence

Wijdenes et al. (2019) conducted a research with the aim of exploring the prevalence and severity of compassion fatigue risk among nurses and to ascertain the differences in demographic characteristics among the participants correlating with the abovementioned risk. Their measures included the Professional Quality of Life version 5 (ProQOL-5) (Stamm, 2009) and their findings were that nearly half of the sample was at risk for moderate to high compassion fatigue. Moreover, nurses' unit was significantly associated with compassion satisfaction while time and experience in service were not protective factors for compassion fatigue. Lastly, secondary traumatic stress, burnout and compassion satisfaction were significantly correlated.

Al-Majid et al. (2018) assessed the degree of compassion satisfaction and compassion fatigue in both care and charge nurses of care units. The measurement was conducted through the ProQOL-5, leading to an average overall result concerning compassion variables with significantly lower compassion satisfaction in less experienced nurses (<10 years of work), while other scales such as secondary traumatic stress showed high levels among charge nurses.

Likewise, Roney and Acri (2018) investigated pediatric nurses' levels of compassion satisfaction, compassion fatigue, and job satisfaction while considering any correlations among the constructs, using the ProQOL-5. Their results found participants with higher than the norm levels of compassion satisfaction and slightly lower than the norm levels of secondary trauma and burnout, highlighting an interesting significant relationship between female gender and the compassion satisfaction subscale.

Allie et al. (2018) focused their cross-sectional analytic study on HCPs' bereavement overload, defined as a situation where an individual must deal with loss or death in a continuous and close way with the unfortunate result of an abnormal adjustment process. Their study investigated through an interviewer-administered questionnaire various quantitative variable such as bereavement overload, compassion fatigue and coping mechanisms. Findings showed that half of the participants reported a suffering from bereavement overload, of which three quarters reported compassion fatigue (especially doctors and final-year medical students). Interestingly, also half of the health providers which didn't show bereavement overload, suffered from compassion fatigue. The authors have deduced that while compassion fatigue may be an effect of bereavement overload it could lead to dysfunctional coping mechanisms such as emotional detachment.

Copeland and Henry (2018) designed a cross-sectional study to survey emergency department staff members with the purpose of examining the relationship between exposure to workplace violence (physical and psychological) and compassion fatigue or satisfaction through the Professional Quality of Life model. The findings of this study showed that all three of the ProQOL dimensions were significantly associated with exposure to violence, particularly with patient threats, name calling, sexual innuendo and threats of lawsuit. Furthermore, as the study described above (Al-Majid et al., 2018), also from their findings the most experienced nurses in the sample reported higher compassion satisfaction, lower burnout and secondary traumatic stress, than those with less experience.

Moreover, with the intention of observing the relationship between burnout, self-esteem and compassion, Erkorkmaz et al. (2018) conducted an analytical cross-sectional study on nurses, finding that burnout was affecting both compassion satisfaction and personal accomplishment (subscale of the Maslach Burnout Inventory) (Maslach et al., 1997) negatively.

Using the Self-Compassion Scale (SCS)-Short Form (Raes et al., 2011) and the Barriers to Physician Compassion Questionnaire (Fernando and Consedine, 2014). Dev et al. (2018) evaluated the associations between burnout and barriers to compassion in a large sample of nurses. Their findings showed the expected association in which higher levels of burnout predicted greater barriers to compassion while higher levels of trait self-compassion were associated with lower burnout and predicted lower barriers to compassion.

About Mindfulness and Compassion Fatigue Correlation

Brown et al. (2017) explored the association between compassion fatigue and mindfulness in mental health professionals, considered that the purpose of the study was to explore whether there is an inverse relationship between the two variables, measured by the Five Facet Mindfulness Questionnaire (FFMQ) (Baer et al., 2008) and the ProQOL-5. The results showed a moderate, negative correlation between compassion fatigue and mindfulness. These findings suggest that high levels of compassion fatigue are associated to lower levels of mindfulness, meaning that mindfulness traits may be helpful in ameliorating compassion fatigue.

Similarly, Olson et al. (2014) collected data regarding burnout, emotional intelligence, empathy, mindfulness, self-compassion and resilience, in pediatric medicine residents of an urban children's hospital. Their measure was carried out also through the FFMQ and the SCS (Neff, 2003) and the results reported a negative association between mindfulness/self-compassion and burnout, with a positive association between the two and resilience factors and less emotional exhaustion. The authors suggest that both mindfulness and self-compassion may protect professionals' personal health and well-being.

Gracia-Gracia and Oliván-Blázquez (2017) analyzed the ability of self-compassion and mindfulness associated to burnout in nurses of intensive care units, also investigating

the relationship between self-compassion as a positive mental state in association with mindfulness. The results of this study showed that compassion variables were predictive for burnout (emotional exhaustion, depersonalization and personal accomplishment), in particular the years of overall professional experience, self-kindness, self-judgement and the humanity-isolation factor of compassion. Furthermore, the mindfulness subscale appeared to have an inverse significant correlation with emotional exhaustion.

The research group of Montero-Marin et al. (2016), while confirming the validity of the burnout subtype model, assessed the explicative power of the self-compassion construct as a protective factor. According to a previous described study (Gracia-Gracia and Oliván-Blázquez, 2017), they used the SCS for this purpose. Their findings were that negative self-compassion dimensions might play an important role in the development of the burnout subtypes in Spanish HCPs, suggesting that negative self-compassion dimensions should be considered as vulnerability factors.

Silver et al. (2018) conducted a research with the aim of assessing relationships between mindfulness and some professional variables such as burnout, compassion fatigue, work engagement, and empathy on genetic counselors that provide immediate clinical aid to patients. They used the Mindfulness Attention Awareness Scale (MAAS) (Brown and Ryan, 2003) to evaluate mindfulness levels and the ProQOL-5 for burnout and compassion fatigue. Their findings showed that half of the participants reported engaging in activities which are typically associated with mindfulness (such as yoga, meditation, or breathing exercises); furthermore, there was a significant positive correlation between empathy/work engagement and mindfulness and moderate negative associations between mindfulness and burnout/compassion fatigue. According to some other studies, the authors suggest that mindfulness could affect positively professional satisfaction and quality of patient care.

Effectiveness of MBSR, Mindfulness-Related, or Compassion-Related Interventions—Pre-post Design Studies

MBSR Intervention

Brady et al. (2012) assessed the impact of the MBSR program on managing work stress and improving patient outcomes in 16 hospital staff members consisting of psychiatrists, psychologists, nurses, social workers, mental health technicians, and activity therapists. The structured 4 week MBSR program was successful in influencing the levels of personal stress, mindfulness, and intrapersonal presence of inpatient psychiatric staff members.

Cohen-Katz et al. (2005) reported results exploring the effects of MBSR on 25 nurses. Treatment group subjects significantly decreased scores on 2 of 3 subscales of the Maslach Burnout Inventory compared to wait-list controls, while within-group comparisons for both groups pre-treatment and post-treatment revealed similar results. Changes were maintained as long as 3 months post-treatment.

Duarte and Pinto-Gouveia (2017) evaluated the effects of an MSBR program on 29 oncology nurses, with respect to 19 nurses of a waitlist comparison condition. Changes in mindfulness mediated changes in burnout, anxiety and stress, and satisfaction with life; changes in self-compassion mediated the influence of the intervention on burnout, depression, anxiety, stress and satisfaction with life; and psychological inflexibility mediated decreases in burnout, compassion fatigue, depression, and stress.

Lamothe et al. (2018) considered the feasibility and acceptability of an MBSR-based intervention and its impact on psychological variables, assessed pre- and post-intervention, like mindfulness, empathy, identification of one's own emotions and those of others, emotional acceptance and recognition of emotions in others, in two studies: in Study 1, 12 students completed the 8 week MBSR program, while in Study 2, 25 HCPs completed the 8 week MBSR program. Participants who completed the program improved on all measures except the identification of others' emotions and empathy.

Wylde et al. (2017) compared the effects of an 8 week MBSR intervention to a smartphone delivered mindfulness intervention, Headspace, an audio-guided mindfulness meditation program, in a group of 95 novice nurses, at the beginning of their internship and 3 months after entering the program, measuring compassion satisfaction, compassion fatigue, burnout, stress, trauma symptoms, and mindfulness variables. Nurses in the smartphone delivered mindfulness group showed significantly more "acting with awareness" and more "non-reactivity to inner experience" skills with respect to the MBSR group. The smartphone intervention group also reported more compassion satisfaction and less burnout. For novice nurses, smartphone delivered mindfulness interventions may be more beneficial.

A controlled mixed methods pilot study (Verweij et al., 2016) investigated the feasibility and effectiveness of MBSR on burnout, empathy, and work-related well-being, assessed before and after the intervention, in 43 general practitioner trainers of two Dutch hospitals. The MBSR group showed a greater reduction in depersonalization than the control group, while mindfulness and dedication increased significantly in the MBSR group than in the control group. There was no significant difference in empathy.

Raab et al. (2015) carried out a pilot study on the effects of an MBSR educational intervention on 22 female mental health professionals' self-compassion, perceived stress, burnout, and quality of life, assessed pre- and post-intervention. Changes in the SCS total score proved to be significant, while, regarding subscales, changes were significant in self-judgment, common humanity, isolation and overidentification.

Mindfulness-Related Interventions

Regarding mindfulness-related interventions, an evaluation of the impact of a group-based training program, known as "Occupational Mindfulness" (OM), on coping strategies and well-being of 34 employees within a disability service was carried out by Brooker et al. (2013). The program was positively evaluated by participants and found to be associated with significant increases in positive affect and the mindfulness facet of observing. Conversely, extrinsic job satisfaction showed

a significant reduction from baseline to post-training, while negative affect, perceived stress, anxiety, and negative emotional symptoms showed a significant increase. Paradoxical increases of negative emotional symptoms are explained by considering that participants were developing higher levels of awareness of their current circumstances, whether positive or negative, internal or external. Mindfulness is not directly related to changing circumstances but about developing awareness to what those circumstances are.

A pre-post qualitative study investigated the effects of short-dose, 1–3 min-guided periods of mindfulness, conducted at the beginning of several staff meetings for 20 health professionals, which comprised social workers, therapists, nurses, doctors, administrative staff and leaders. The mindfulness facilitators were interviewed before the intervention and predicted that their groups would experience numerous intra- and interpersonal benefits. After implementation, they showed all of these benefits (Duggan and Julliard, 2018).

Farina et al. (2018) induced professional nurse educators to offer a 10–12 min mindfulness experiential learning session, during the institute's annual professional development forums, to 545 nurses. The nurse educator shared a biofeedback card and survey and asked the nurses to obtain and document their pre-practice and post-practice biofeedback card color and conclude the survey. The difference in the self-reported biofeedback card colors, indicating calm or relaxed states before and after the session, was significant.

Fernando et al. (2017) evaluated whether a brief mindfulness intervention increased compassionate responding to difficult patients and assessed whether the self-compassion trait moderated the impact of this experimental manipulation in a sample of 83 medical students. The intervention elicited mindfulness equivalently at both high and low levels of self-compassion. Furthermore, mindfulness predicted greater patient "liking" and "caring," but only among students lower in self-compassion, while mindfulness predicted greater helping behavior, but primarily among students with higher self-compassion.

The Mindful Nursing Pilot Study (Horner et al., 2014) was a quasi-experimental research where 46 nurses belonging to a nursing unit participated in the 10 week mindfulness training program while an additional nursing unit served as the control group. Classes were held once a week and lasted 30 min. The group that underwent the intervention showed improvement in levels of mindfulness, burnout, and stress as well as patient satisfaction (though mindfulness and burnout scores did not reach significance) while the control group showed no significant differences.

Klatt et al. (2017) administered a brief experiential introduction to mindfulness to 286 HCPs, including dieticians, nurses, psychologists, and smoking cessation educators, measuring, during the meetings and at 3 month follow-up, participant's previous awareness and use of Complementary and Alternative Medicine techniques, and consequent probability of deepening the knowledge of these modalities for personal and professional use. Immediately after the experiential introduction 94.79% of respondents reported a probability to deepen the knowledge of mindfulness for personal use and 92.58% for professional use, while, at 3 month follow-up, 58% had used mindfulness personally and 28% reported that they had used mindfulness techniques professionally.

Pakenham (2015) investigated the effects of an Acceptance and Commitment Therapy (ACT) training, 12 2 h weekly workshops, on stress, therapist skills and characteristics, and the personal acquisition of ACT strategies in 32 clinical psychology trainees that completed measures of work-related stress, psychological distress, self-compassion, counseling self-efficacy, client-therapist alliance, acceptance and action, mindfulness, thought suppression and values, before and after university-based ACT training. Results showed that clinical psychology trainees reported improvements from before to after training on measures of counseling self-efficacy, client–therapist alliance, self-kindness, acceptance, defusion, mindfulness and values, and a marginally significant improvement on somatic symptoms, despite a trend toward increased work-related stress.

A pilot study (Pflugeisen et al., 2016), using a single-sample, pre-post study design, evaluated the feasibility of implementing an 8 week video-module based mindfulness pilot program aimed to reduce stress, ameliorate well-being, and develop mindfulness skills in 23 physicians in a community hospital setting. Participants experienced three 90 min in person trainings, weekly online video-module trainings, and weekly teleconference coaching calls. Physician stress, well-being (emotional exhaustion, depersonalization of patients, sense of personal accomplishment), and mindfulness skills (observing, describing, acting with awareness, acceptance without judgment) were evaluated. Significant reductions in stress, personal accomplishment, and emotional exhaustion and improvements in all mindfulness skills were observed at end-of-program.

Sansó et al. (2018), in a pre-post pre-experimental study, evaluated the outcome of a 6 week mindfulness training program on mindful attention, self-compassion, and professionals' quality of life in 36 HCPs of palliative care teams. After the intervention, there was an improvement of mindfulness, self-compassion, and burnout risk levels lowered, regardless of the profession.

Steinberg et al. (2016) explored the feasibility of a workplace intervention for improving resilience to stress of 32 of surgical intensive care unit HCPs, randomly assigned to an intervention or control group. The intervention consisted of a MBI including meditation, mild yoga movement, and music and was carried out in a group format 1 h a week for 8 weeks. Measures of burnout, compassion satisfaction, compassion fatigue and work engagement were obtained before and after the intervention. Work satisfaction improved significantly in the intervention group with no difference in the control group. Participants reported that recognizing their stress response was a main benefit of the intervention.

The study conducted by Taylor et al. (2016) examined the feasibility and impact of a 10 day mindfulness meditation intervention on 33 pediatric residents using a free smartphone application, Headspace. Measures of burnout and mindfulness were administered before and after the intervention. After the intervention, an increased percentage of residents perceived mindfulness as a useful intervention for patients and there was

a significant increase in the number of residents who planned to discuss mindfulness as a therapeutic option for their patients, while there were no changes in burnout scores.

A field study (Wacker and Dziobek, 2018) evaluated a 3 day employee training in non-violent communication on non-violent communication skills, cognitive and emotional empathy, empathic distress and perceived social stressors at work in 29 HCPs. Participants filled out questionnaires before and 3 months after training. Results showed that communication skills were fostered in training participants, evidenced by the higher levels of emotion verbalization behavior and the enhanced use of non-violent communication at work. Empathic distress decreased, and the elevation of social stressors at work was hindered by enhanced emotion verbalization.

Wahl et al. (2018) aimed to conduct a peer support network pilot project through the inclusion of education/training, peer support and resiliency training and to investigate how interventions impact compassion satisfaction and compassion fatigue of 20 nurses, working in a community hospital, that completed pre-intervention and 6 week post-intervention surveys. Results revealed statistically significant improvements in compassion satisfaction and non-significant improvements in compassion fatigue.

Ofei-Dodoo et al. (2020) examined a group of 43 HCPs that participated in 8 week workplace, group mindfulness-based yoga intervention. Participants completed online measures regarding depression, anxiety, stress, resilience, burnout, and compassion at baseline and post-intervention. After the intervention, HCPs showed significant improvements on personal accomplishment, depression, anxiety, stress, perceived resilience, and compassion.

Compassion-Related Interventions

Thirteen nursing professionals underwent a stress reduction program, including mindfulness and loving kindness meditation. Quality of life assessment revealed significant increase as well as perceived stress, burnout, depression, and trait anxiety, while self-compassion did not show significant differences (Santos et al., 2016).

An observational, mixed-method pilot evaluation study (Orellana-Rios et al., 2017) enrolled 28 staff members of an interdisciplinary palliative care team and explored the feasibility and effectiveness of a 10 week group program with four aims: development of a mindful presence, cultivation of loving-kindness, Tong-len practice in difficult situations and the integration of these practices into daily work occupations. The investigated variables were burnout, perceived stress, anxiety, depression, somatization symptoms, emotion regulation, perceived job situation and goal attainment. Significant ameliorations were found in two of three burnout components (emotional exhaustion and personal accomplishment), anxiety, stress, two emotional regulation competences and joy at work. In addition, 85% of the individual goals were achieved.

A pilot study (Pfaff et al., 2017), with an embedded experimental mixed-methods design, evaluated the impact of 6 week formalized pilot compassion fatigue resiliency intervention on 32 HCPs participants at a regional cancer center. The impact of the intervention, in a pre- and post-intervention design, was evaluated on compassion fatigue and satisfaction, burnout, clinical stress and silencing responses. Participants showed diminished clinical stress at intervention completion, but no other overall changes.

Effectiveness of MBSR, Mindfulness-Related or Compassion-Related Interventions—Cohort Design Studies

MBSR Intervention

Eliassen et al. (2016) examined the effect of two different training programs, namely two 8 week interventions of mindfulness training and affect-consciousness training, on mindfulness and on the perception of the ward atmosphere of two groups of HCPs, consisting of 27 and 23 participants, respectively. Measurements were taken at two baseline time points and four times following the intervention. Findings in this study indicate that MBSR staff training may give rise to beneficial changes in measures of Support, Program Clarity and Anger and Aggressive Behavior, as indicated by the Ward Atmosphere Scale (WAS) (Røssberg and Friis, 2003) subscales, suggesting that the MBSR intervention may modulate staffs' manner of relating to patients. Conversely, affect-consciousness staff training, as measured with the WAS, may strengthen Order and Organization, with an enduring effect up to 6 month follow-up. Differences on different subscales on the WAS may indicate that the affect-consciousness intervention is different in its effect as compared to the MBSR.

Mindfulness-Related Interventions

Research by Kemper's research group mainly investigated the impact of brief online mindfulness training on mindfulness and other psychological variables of HCPs. Kemper (2016) analyzed data from 178 HCPs and trainees who completed self-reflection exercises included in online mindfulness training, including three 1 h modules: introduction to mindfulness, mindfulness in daily life and mindful breathing and walking. Outcome data was related to mindfulness, measured with the Cognitive and Affective Mindfulness Scale–Revised (CAMS-R) (Feldman et al., 2006), the MAAS and the FFMQ. Concluding a brief, online training was associated with small but significant improvements in mindfulness scores, measured by all the three tools. In addition, there were no changes in improvement by gender, among the different HCPs. In a related prospective cohort study, Kemper and Rao (2016) investigated the effects of an online training program related to focused attention meditation, including three 1 h modules (introduction to stress, resilience and the relaxation response, clinical effects of the relaxation response and physiological effects of the relaxation response) on resilience, relaxation, stress, positive and negative affect and flourishing variables, assessed before and after training, of 379 HCPs. Even brief, online training was associated with small but significant improvements in relaxation, resilience, stress, positive and negative affect, and flourishing.

Luthar et al. (2017) reported on the effects of an intervention to foster resilience among women health care providers who

are mothers at high risk for stress and burnout. 40 mothers were assigned randomly to either 12 weekly 1 h sessions of a structured, relational supportive intervention, the Authentic Connections Groups, including minimizing rumination, "good enough" mothering and shame (Carmassi et al., 2017a) vs. self-compassion, or to 12 weekly hours to be used as needed. Participants were evaluated at baseline, after the intervention, and 3 months follow-up on general symptomatology, depression, self-compassion and burnout plus plasma cortisol. After the intervention, results showed higher levels of improvements for mothers in the Authentic Connections Groups than control condition for depression and global symptoms. By 3 months follow-up, significant changes were found for depression and global symptoms and self-compassion, feeling loved, physical affection received, and parenting stress. Participants in the Authentic Connections Groups (but not control group) condition also showed significantly diminished cortisol levels at both after the intervention and follow-up.

O'Mahony et al. (2017) evaluated the preliminary outcomes of a group-based 9-session multimodal mindfulness training pilot designed to improve indicators of burnout and mental health symptomatology in 13 health care providers who interact with children in the context of end-of-life care. Measures were assessed before the program, at the program midpoint, and at the end of the program and were PTSD symptomatology, experiential avoidance, cognitive fusion, depression and burnout. Results revealed significant improvements in depressive and PTSD symptoms among HCPs.

Riley et al. (2016) carried out two studies to compare the impact of Cognitive Behavioral Stress Management (CBSM) and an 8 week Yoga-Based Stress Management (YBSM) interventions for HCPs. Study 1 evaluated YBSM intervention in 37 mental HCPs and gathered data regarding depression, anxiety, stress, health-related quality of life, coping skills, emotion regulation, mindfulness and self-compassion, pre- and post-intervention. Study 2 investigated YBSM and CBSM in 40 randomly assigned mental health care providers and collected data regarding depression, anxiety, stress, health-related quality of life, burnout, coping skills, and general health data at four time points. Results of Study 1 showed statistically significant increases in relaxation, coping confidence, self-kindness, self-compassion, general mental health, general physical health, and mindfulness, while results of Study 2 showed significant improvement in compassion satisfaction, depression, stress, heart rate, alcohol consumption, and burnout.

Suyi et al. (2017) examined the efficacy of a 6 week mindfulness program in improving mindfulness, compassion and self-compassion, and diminishing perceived stress and burnout, among 37 mental HCPs in Singapore. The program comprised 2 h sessions offered once a week and utilized a range of mindfulness techniques to instruct participants to cultivate compassionate and non-judgemental attitudes toward their inner experiences. Data was gathered at three time-points: pre- and post-intervention, and a 3 months follow-up. Participants showed significant amelioration in four of the five mindfulness domains (observe, describe, non-judge, non-react) and in compassion and self-compassion levels, and a significant decrease in stress, following mindfulness intervention. The improvements in mindfulness and self-compassion levels were maintained at three months follow-up. No significant difference was observed for burnout variables.

Wen et al. (2017) assessed how the self-guided, smartphone-based mindfulness app, Headspace, affects mindfulness, stress and negative emotions variables in 43 medical residents. Measures were collected before the intervention, at the midpoint (after 15 days), and at the end of the intervention (after 30 days). Results showed that both the mindfulness and positive affect scores showed a significant improvement with increasing use of the app, while the negative affect score did not show significant change.

Compassion-Related Interventions

Kemper et al. (2015) assessed the impact of online Mind-Body Skills (MBS) training on clinicians' and trainees' stress, mindfulness, and confidence in providing calm, compassionate care. MBS training (http://mind-bodyhealth.osu.edu) contained 12 1 h modules of continuing medical education–approved material organized in 4 general topics: focused attention meditation (relaxation response), mindfulness meditation, positive affect meditation (positive or sacred word, gratitude, and loving-kindness/compassion meditation) and guided imagery/hypnosis (autogenic training; guided imagery to prepare for surgery, procedures, or childbirth; and guided imagery for sleep and changing habits). Participants who engaged in MBS significantly improved in measures of stress, mindfulness, and confidence in offering calm, compassionate care. In a related prospective cohort study, Kemper and Khirallah (2015) assessed the effects of MBS training on mindfulness, resilience, and empathy of 513 HCPs. Completion of MBS training was related with significant ameliorations in stress, mindfulness, empathy and resilience, suggesting that this training is able to reach diverse HCPs.

Scarlet et al. (2017) studied the effects of an 8 week Compassion Cultivation Training (CCT) (Jazaieri et al., 2013) on work-related burnout, interpersonal conflict, mindfulness, self-compassion, fear of compassion and job satisfaction scores of 62 HCPs. The questionnaires were administered by email during the first, middle, and last weeks of CCT, as well as 1 month follow-up. Results showed significant improvements in participants' self-compassion, mindfulness, and interpersonal conflict levels.

DISCUSSION

This systematic review summarized the evidence regarding mindfulness- and compassion-related qualities of HCPs as well as potential effects of MBSR, mindfulness-related and compassion-related interventions on professionals' psychological variables like mindfulness, compassion, self-compassion and quality of life. The number of articles that met the inclusion criteria was 57 (4 RCTs, 23 studies with pre-post measurements, 12 cross-sectional studies, 11 cohort studies and 7 qualitative studies).

Qualitative Studies

In regard of the qualitative studies, most of them investigated the relationship between mindfulness and compassion dispositions with burnout, stress levels, positive workplace relationships, and individualized patients care (Platt et al., 2015; Lyddy et al., 2016; McPherson et al., 2016; Hunter et al., 2018; Powell et al., 2018). From the examined studies, mindfulness dispositions appeared to be important in the fight against burnout and to manage effectively the stress response (Platt et al., 2015). Moreover, HCPs would seem to benefit more from the use of informal practices than from formal ones (Lyddy et al., 2016). As a result, the suggestion that we could gain from this information collection is to effectively increase mindfulness training in healthcare settings and provide professionals with less formal tools to tackle their job.

Randomized Controlled Trials

With regard to the RCT studies, we highlight that MBSR or mixed mindfulness interventions resulted to be more effective than controls in samples of doctors and HCPs in three of the four examined researches. In particular, mindfulness interventions were most effective on stress (Amutio et al., 2015; Ireland et al., 2017), job burnout (Amutio et al., 2015; Ireland et al., 2017), and safety compliance at work (Valley and Stallones, 2017). Amutio et al. (2015) also highlighted the importance of a maintenance programme after the mindfulness intervention.

Cross-Sectional Design Studies

With reference to the cross-sectional selected studies, we observed various researches linking compassion fatigue/compassion satisfaction (risk and prevalence) with violence exposure, coping mechanisms, burnout and bereavement overload (Brown et al., 2017; Allie et al., 2018; Copeland and Henry, 2018). With respect to this topic, the results obtained are somewhat controversial; on the one hand, we observed a confirmation of a high presence of burnout, compassion fatigue and secondary traumatic stress in the investigated samples. On the other hand, many studies have observed internal variations concerning these variables, depending on gender or years of experience at work (Al-Majid et al., 2018; Roney and Acri, 2018; Wijdenes et al., 2019). Supposing that compassion fatigue is a consequence of burnout, some studies have also pointed out the positive correlation between burnout and compassion barriers or between bereavement overload and emotional detachment (Gracia-Gracia and Oliván-Blázquez, 2017; Dev et al., 2018). These findings should elicit some reflections on the role played by the excessive stress load on the behavior of health personnel, redesigning both the therapeutic and interventional approach to this topic.

Moreover, as far as correlation between mindfulness and compassion is concerned, findings show that mindfulness approach may be useful in mitigating the negative aspect of compassion fatigue, which is, in turn, predictive for burnout (Brown et al., 2017). Consequently, both mindfulness and compassion satisfaction represent a protective factor on the HCPs' well-being and quality of patient care. Mindfulness also demonstrated a positive correlation with resilience, empathy, work engagement, and less emotional exhaustion (Olson et al., 2014; Silver et al., 2018). Finally, these findings should elicit a reflection about the negative impact of self-compassion dimensions, which could be studied as a vulnerability factor.

MBSR and Mindfulness-Related Interventions

Regarding pre-post design research, 7 studies investigated the effects of MBSR intervention on HCPs. MBSR proved to be effective in maintaining (Cohen-Katz et al., 2005) or improving mindfulness levels (Brady et al., 2012; Verweij et al., 2016; Duarte and Pinto-Gouveia, 2017; Lamothe et al., 2018), and an MBSR educational intervention was effective at improving self-compassion levels (Raab et al., 2015). In novice nurses, a smartphone-delivered audio-guided mindfulness meditation program, Headspace, resulted in more acting with awareness compared to the MBSR group (Wylde et al., 2017). It may be hypothesized that for novice meditators, that are approaching mindfulness, a progressive approach to meditation may be helpful. In a cohort study, MBSR seems to promote beneficial changes in measures of support, program clarity, anger and aggressive behavior suggesting that the MBSR intervention may be helpful at regulating staffs' relational abilities with patients (Eliassen et al., 2016).

Studies employing intervention protocols that were different from standard MBSR, were carried out with very different mindfulness-related interventions. Interventions that were found to be effective at improving mindfulness levels were 1–3 min-guided periods of mindfulness (Duggan and Julliard, 2018), 10 min mindfulness induction exercises (Fernando et al., 2017), a 10 day mindfulness meditation intervention using a free smartphone application (Headspace) (Taylor et al., 2016), 6 week mindfulness training (Sansó et al., 2018), an 8 week video-module based mindfulness program (Pflugeisen et al., 2016) and an ACT training (Pakenham, 2015), while a 10 week mindfulness training program, the Mindful Nursing Pilot Study, resulted in mindfulness improvements that were not statistically significant (Horner et al., 2014), possibly because of sessions that lasted 30 min, instead of 60 or 90 min. OM was found to increase positive affect and the mindfulness facet of observing together with a paradoxical increase of negative emotional symptoms, possibly due to a greater awareness of participants current circumstances (Brooker et al., 2013). An 8 week MBI was found to be effective on work satisfaction but not on compassion satisfaction or compassion fatigue (Steinberg et al., 2016), while a peer support network pilot project resulted in statistically significant improvements in compassion satisfaction and non-significant improvements in compassion fatigue (Wahl et al., 2018). An 8 week supervised workplace, group mindfulness-based yoga intervention was able to improve compassion levels (Ofei-Dodoo et al., 2020), while A 3 day employee training in non-violent communication was able to reduce empathic distress (Wacker and Dziobek, 2018) and a brief experiential introduction to mindfulness increased the

likeliness to investigate, or to use, mindfulness for personal or for professional use (Klatt et al., 2017). Ten to twelve minutes of mindfulness experiential learning session was found to produce a statistically significant difference in the self-reported biofeedback card colors indicating calm or relaxed states before and after the session (Farina et al., 2018). Analogously, cohort studies showed that mindfulness-related interventions were found to be effective at improving depression, global symptoms, self-compassion, feeling loved, physical affection received, parenting stress, and cortisol levels (Luthar et al., 2017), at reducing depressive and PTSD symptomatology (O'Mahony et al., 2017), at improving compassion satisfaction, depression, stress, heart rate, alcohol consumption and burnout (Riley et al., 2016) and at increasing four of the five mindfulness domains (observe, describe, non-judge, non-react) and compassion and self-compassion levels (Suyi et al., 2017). Kemper's research group investigated the effects of a brief online mindfulness training that was able to improve mindfulness scores, measured by CAMS-R, MAAS, and FFMQ (Kemper, 2016), and relaxation, resilience, stress, positive and negative affect, and flourishing (Kemper and Rao, 2016), while the smartphone-based mindfulness app, Headspace, was able to increase mindfulness and positive affect scores (Wen et al., 2017).

Compassion-Related Interventions

Compassion-related interventions, that mainly included loving-kindness meditation (Santos et al., 2016; Orellana-Rios et al., 2017) or a formalized pilot compassion fatigue resiliency intervention (Pfaff et al., 2017), were found to be effective at improving quality of life (Santos et al., 2016), burnout components of emotional exhaustion and personal accomplishment (Orellana-Rios et al., 2017) and at reducing clinical stress (Pfaff et al., 2017). No other main significant changes were observed. In cohort studies, Kemper's research group found that online MBS training was effective at significantly improving stress, mindfulness, and confidence in providing calm, compassionate care (Kemper et al., 2015) and at providing significant ameliorations in stress, mindfulness, empathy and resilience (Kemper and Khirallah, 2015). CCT (Jazaieri et al., 2013) was found to significantly enhance participants' self-compassion, mindfulness, and interpersonal conflict scores (Scarlet et al., 2017).

MBSR, Mindfulness,- and Compassion-Related Interventions

Taken together these results suggest that MBSR intervention is able to improve, and maintain, mindfulness levels, self-compassion levels and to improve burnout, depression, anxiety, stress (Lamothe et al., 2016). MBSR intervention has been shown to be able to modulate anger and aggressive behavior as well, with a suggestion that a smartphone-delivered audio-guided mindfulness meditation program, Headspace, may be helpful for novice HCPs.

The most frequently employed interventional strategies were mindfulness-related trainings (Fox et al., 2018) that proved to be effective at improving nurses' mental health significantly (Guillaumie et al., 2017), for treating burnout in occupational therapy professionals (Luken and Sammons, 2016) and at reducing stress among HCPs (Burton et al., 2017). Overall, as also outlined by West et al. (2016), mindfulness-related interventions, even of brief duration (Gilmartin et al., 2017), were effective at improving mindfulness levels, self-compassion, depression, global symptoms, feeling loved, physical affection received, parenting stress, cortisol levels, work and compassion satisfaction and at increasing the likeliness to investigate, or to use, mindfulness for personal or for professional use, but not at improving compassion fatigue (Steinberg et al., 2016; Wahl et al., 2018). Though the true prevalence of burnout (Rotenstein et al., 2018), compassion fatigue, secondary traumatic stress and vicarious trauma in HCPs (Mol et al., 2015) remains open for discussion, compassionate care is fundamental for better clinical and patient outcomes, but during healthcare provision it can be hampered by several factors. It has been highlighted that stress and negative affect, on which MBSR is particularly effective (Lamothe et al., 2016), were moderately positively associated with compassion fatigue, and that positive affect also had a moderately positive relationship with compassion satisfaction (Zhang et al., 2018). As for the neurobiological studies (Hölzel et al., 2013; Taren et al., 2013, 2015; Engen and Singer, 2015), mindfulness seems to be effective at improving negative affect and, possibly, compassion fatigue, while compassion satisfaction may be related to cultivation of positive affect. In this regard, CCT (Jazaieri et al., 2013; Scarlet et al., 2017) and MBIs (Wasson et al., 2020) have been shown to improve participants' self-compassion, mindfulness, and interpersonal conflict scores.

Remarkably, Egan et al. (2019) reported that HCPs are aware of the burnout potential and their experiences of the necessity to access help to cope with a demanding environment. However, HCPs were not tired of being compassionate (compassion fatigue), but rather, tired of having to overcome the organizational barriers to being compassionate. Participants did not state that they were tired of caring, but they were tired of not being able to care as they would like to. In this regard, MBSR, mindfulness- and compassion-related interventions may prevent HCPs' burnout and promote their enduring compassion and caring.

LIMITATIONS AND FUTURE RESEARCH

The search strategy used in this review limited the search with the inclusion criteria of English or Italian language and peer-reviewed articles only. Consequently, though an extensive search was carried out, it is not correct to claim that the review is exhaustive given the papers excluded that were written in other languages or articles published in other formats (e.g., unpublished theses).

Despite these limitations, this systematic review presents a synthesis of mindfulness and compassion characteristics of the healthcare professionals and of MBSR, MBIs, and CBIs that have been delivered specifically to this professional population. Findings of the review depict the potential of MBSR, MBIs and CBIs as a tool for enhancing professionals' mindfulness, self-compassion and quality of life. Considering

the differences of methodological approach and intervention protocols of the existing MBSR, MBIs, and CBIs studies, for future research it may be suggested to carry out studies that combine structured mindfulness and compassion cultivation trainings (e.g., mindful self-compassion program; Neff and Germer, 2013) to enhance the effects of interventions, to limit the variability of intervention protocols and to improve data comparability.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

AUTHOR CONTRIBUTIONS

CC designed and executed the study, assisted with the data analyses, and wrote the paper. RC collaborated with the design and writing of the study. GO analyzed the data and wrote part of the results. AG and MD collaborated in the writing and editing of the final manuscript. AP collaborated with the design and writing of the study. All authors approved the final version of the manuscript for submission.

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frontiers in Psychiatry

ORIGINAL RESEARCH
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Preliminary Reliability and Validity of the DMRS-SR-30, a Novel Self-Report Measure Based on the Defense Mechanisms Rating Scales

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Defense mechanisms are psychological factors that influence emotional distress and quality of life. There are a number of measures assessing the construct of defense mechanisms, but only few available instruments reflect the gold-standard theoretical hierarchical organization of defenses. We report on the development of a novel 30 item self-report questionnaire, the DMRS-SR-30, based on the parent instrument, the Defense Mechanism Rating Scales (DMRS). This study tested preliminary reliability and validity of the Italian version of the DMRS-SR-30. We first extracted 30 items from the DMRS Q-sort version (DMRS-Q) and adapted them for a self-reported format. We then applied the DMRS quantitative scoring algorithms to provide proportional scores for the 28 individual defenses and summary scores for seven defense levels and overall defensive functioning (ODF) scores. A dynamic interview was used for assessing participant's defense mechanisms with the observer-rated DMRS and DMRS-Q. We examined internal consistency of the scales along with criterion, concurrent, convergent and discriminant validity among participants (N = 94) who completed the DMRS-SR-30, SCL-90, BDI, and IES-R. Results showed very good internal consistency for ODF (Cronbach's alpha = .890) and the high adaptive defense level, whereas some subscales with few items had lower values. Correlation analyses between DMRS-SR-30 and the two DMRS-based observer-rated measures showed very good criterion and concurrent validity for ODF and moderate to high for defense levels subscales. Correlations between the DMRS-SR-30 ODF and SCL-90 GSI, BDI and IES=R (r = –.456, r= –.540, r = –.402, respectively, all p <.001), indicated good convergent validity. Despite the well-known limitations of self-report methods of psychodynamic phenomena, self-report measures are highly practicable for assessing large samples. The DMRS-SR-30 is the first self-assessed measure describing the whole hierarchy of 28 defense mechanisms and providing scores for ODF, defensive categories, defense levels, and individual defenses. Preliminary examination of the Italian version of the DMRS-SR-30 showed promising results of internal consistency, criterion

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and concurrent validity, and convergent validity and of the measure. Further validation is needed to confirm these findings and explore other aspects of validity and reliability.

Keywords: DMRS-SR-30, reliability, validity, defense mechanisms, psychological distress, quality of life, self-report measures

INTRODUCTION

The construct of defense mechanisms was originally developed by Sigmund Freud (1) to explain symptom formation from the psychoanalytic perspective. This concept was further conceptualized by Anna Freud as adaptive ego strategies that enables the mind to reach compromise solutions to conflicts that the individual is unable to resolve (2). More than a century of theory and research advances have demonstrated that defense mechanisms are relevant to understand personality functioning, the development of ego strengths, subjective reaction to stress, physical and mental health conditions, quality of relationships, and therapeutic process outcome (3–11). Several studies demonstrated that the progression of chronic medical conditions is associated with the patient's psychological responses to illness-related stress (12–22), which can also indirectly affect psychological well-being of the patient's caregivers (23, 24). The risk of developing and exacerbating psychological distress is particularly relevant in the time of the ongoing COVID-19 pandemic, which is proven to have significant clinical consequences psychological distress and post-traumatic symptoms observed in both general and clinical populations (25–28). Accompanying their widely demonstrated relevance, the assessment of defense mechanisms has attained the interest of psychologists and psychiatrists from different background, necessitating the development of reliable and valid measures for their assessment (29–33). Despite remarkable research progress in defense mechanisms assessment done in the past decades (34–38), only few measures refers to the gold-standard theory of defense mechanisms hierarchy proposed clearly by Vaillant (39–41), and operationalized in the Defense Mechanisms Rating Scales (42, 43) and its recent Q-sort version (DMRS-Q) (44). One available self-report attempting to measure the entire range of defense mechanisms is the well-known Defense Style Questionnaire (36, 45), which despite its poor face validity of shortened version (46) is still the largest used measure for defense mechanisms assessment. The present study describes the development of the novel 30-item DMRS Self-Report (DMRS-SR-30) and shows an initial examination of its reliability and validity.

Based on the hierarchical organization of defense mechanisms (39–42), the DMRS and DMRS-Q are observer-rated measures that provide definition, function, and assessment procedures for 30 defense mechanisms organized into seven defense levels, which are hierarchically ordered based on their general level of adaptiveness in dealing with stress and conflict (47). These instruments also provide an index of overall defensive functioning (ODF) that reflects an overall summary measure, indicating the individual's level of defensive maturity (48–51). Validity and reliability of the DMRS have been widely demonstrated (52–54), as well as its usefulness in tracking change with treatment (55–59) while DMRS-Q validation needs further investigation (44, 60).

DMRS-based measures have been used as comprehensive methods for assessing defense mechanisms providing empirical evidence of the relevance of defense mechanisms assessment (61–64). However, applying either DMRS or DMRS-Q to large sample studies would be extremely expensive in terms of time required for data collection, interview transcription, training of raters and related costs. In these cases, self-report measures become essential, as they can reach participants on large scale, although results could be biased by the individual's lack of awareness of personal defensive activity (65, 66).

Measure Development

The outset of the pandemic and subsequent stay-in-place order in Italy presented the need and opportunity to assess the relationship between distress and psychological resources to cope with the situation. In response, two of the authors (JCP and MDG) developed a 30-item self-report version of the Defense Mechanism Rating Scales. The measure was initially examined on a large Italian survey sample (28) at the outset of the lockdown in Italy. The main aim in developing the DMRS-SR-30 was to provide a self-report measure that represented the whole hierarchy of defense mechanisms as described by the DMRS (42). To facilitate the item formulation, we selected 30 items from the DMRS-Q-sort and adapted them for self-report format. Because some defense mechanisms could not be described adequately by one item only, we instead selected two items each for passive aggression and dissociation. On the other hand, defense mechanisms as idealization of self and other's image and devaluation of self and other's image could be grouped together, thus we selected one item each to represent both forms of idealization and devaluation without distinguishing toward who the image distortion is directed. Similar to the existing observer-rated DMRS assessment methods, the DMRS-SR-30 provides quantitative scoring for ODF, defense categories and levels and individual defenses (see **Table 1**).

Aims

In the present study we aimed to test reliability and validity of the Italian version of the DMRS-SR-30. Specifically we examined: 1) the internal consistency of the DMRS-30 summary scores; 2) the criterion and concurrent validity of the DMRS-SR-30 by comparison to the DMRS (criterion measure), and the DMRS-Q-sort (concurrent measure); and 3) convergent and discriminant validity with symptom measures, including psychological distress, depression and post-traumatic symptoms.

TABLE 1 | 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30) quantitative scoring system.

	Defensive Category	Defense Level	Defense Mechanism
Overall Defensive Functioning (ODF)	Mature	High adaptive	affiliation altruism anticipation humor self-assertion self-observation sublimation suppression
	Neurotic	Obsessional	intellectualization isolation of affect undoing
		Neurotic[b]	displacement dissociation reaction formation repression
	Immature[a]	Minor image-distorting	devaluation idealization omnipotence
		Disavowal	denial projection rationalization autistic fantasy
		Major image-distorting	projective identification splitting of self-image splitting of other's image
		Action	acting out help-rejecting complaining passive aggression

[a]*The Immature category includes two categories of Depressive and Other immature (or nondepressive) defenses. Depressive category includes all Action and Major image-distorting defenses, plus projection and devaluation. Other immature category includes autistic fantasy, rationalization, denial, omnipotence, and idealization.*

[b]*The Neurotic defense level includes two sublevels of Hysterical and Other neurotic defenses. Hysterical defense are Repression and Dissociation, while Other neurotic defenses are Displacement and Reaction Formation.*

METHODS

Sample

We collected a convenience sample of 94 subjects who offered informed consent to participate in the study. Participants were prevalently female (*N*= 58; 62%) with an average age of 25.5 years (*SD*= 9.78), mostly students (N=61; 65%), living at parents' home (N=70; 74%), unmarried (N=76; 81%), and not having children (N=80; 85%). At the time of the interview, they all lived in Tuscany, Italy and have experienced lockdown in the past two months. Inclusion criteria were set as following: being at least 18 year of age; having signed an informed consent for participation in the study; and absence of psychosis and intellectual disabilities.

Measures

Observer-rated and self-report instruments were both used for this validation study.

The Defense Mechanisms Rating Scale (DMRS) (42) is an observer-based method that identifies any of 30 individual defenses as they occur in verbatim interview transcripts. The defenses are hierarchically arranged in 7 defense levels based on similarity of function and level of adaptiveness. The DMRS provides a definition for each defense mechanism, a description of its intrapsychic function, and criteria for discriminating a defense from near-neighbor defenses. Defense levels can be combined into categories of Mature Neurotic and Immature, and the latter is further divided into depressive and nondepressive defenses (**Table 1**). The DMRS convergent and discriminant validity is good for the overall hierarchy of defense mechanisms (53) and inter-rater reliability between trained raters is high for the ODF and defense levels (intraclass R values > 0.80), slightly decreasing lower for individual defenses (intraclass R values between 0.50 and 0.60) (52).

The Defense Mechanisms Rating Scale Q-sort (DMRS-Q) (44) is a computerized observer-rated method based on the DMRS. It provides qualitative and quantitative assessment of 30 defense mechanisms, seven defense levels, and ODF. As the DMRS, the DMRS-Q is based on the hierarchical organization of defense mechanisms described in **Table 1**. The DMRS-Q assessment requires to rank-order 150 items into a seven-rank forced distribution and is available online (https://webapp.dmrs-q.com/login). Preliminary validation studies have found good convergent validity and reliability of quantitative scores. Correlations between DMRS and DMRS-Q ranged from acceptable to excellent (0.72 to 0.92) for both the ODF and the three super-categories of defenses (44). Inter-rater reliability was good for the ODF and defense levels (intraclass R values > 0.80), decreasing to acceptable for individual defenses (median ICC= 0.62).

The Symptom Checklist 90 (SCL-90) (67) is a 90-item self-report assessing psychiatric symptoms and a Global Severity Index (GSI) of psychological distress. The 90 items in the questionnaire are scored on a five-point Likert scale, indicating the rate of occurrence of nine different symptoms during the past weeks. It has been shown to have a good reliability and high internal consistency for all subscales. Validity and reliability of the scale are well-documented (68, 69).

The Beck Depression Inventory (BDI) (70) is a 21-item self-report rating inventory that measures characteristic attitudes and symptoms of depression. It presents questions on specific depressive symptoms and asks respondents to rate their occurrence, using four alternatives varying from "rarely" through "often." The sum of all the item scores yields the BDI Total score. Internal consistency for the BDI ranges from.73 to.92 for psychiatric and nonpsychiatric populations (70, 71).

The Impact of Event Scale-Revised (IES-R) (72) is a 22-item scale assessing posttraumatic symptoms with three subscales reflecting intrusion, avoidance, and hyperarousal. The IES-R has performed well as a screening instrument for PTSD, and has demonstrated concurrent and discriminant validity, as well as a lack of social desirability effects (73).

Procedure

According to the current government lockdown rules at the time we ran the study, all data were collected remotely. Interviewers were undergraduate students trained by the leading author in using a validated structured interview for personality assessment, the Clinical Diagnostic Interview (74), which averaged 30 min in length. Participants were contacted through social media groups

to which the interviewers belonged (e.g. Facebook, Instagram, Twitter followers). They were informed about the aims of the study and asked to sign an informed consent to participate to this research. Interviewers provided a link to respond to a survey including socio-demographic information, defense mechanisms, depression, and posttraumatic symptoms. Due to the length of the measure used for assessing psychological distress, which included 90 items per se (67), a second link was created and sent to participants within 2 days from sending the survey link. Simultaneously, they arranged an appointment for the interview-call, each of which was audio-recorded and transcribed verbatim. Finally, three raters were trained in the use of the DMRS and the DMRS-Q. Two among the three randomly selected raters blindly and independently rated either the DMRS or the DMRS-Q from the interview transcript and their ratings were used for data analyses.

Statistical Analyses

Reliability, measured as internal consistency, was calculated with Cronbach's alphas test on ODF, defensive categories and defense levels. Spearman rho correlation analyses were used to test criterion validity, while Pearson correlation analyses were used to test concurrent, convergent and discriminant validity. We compared DMRS-SR-30 quantitative scores with DMRS and DMRS-Q to test Criterion and concurrent validity of the DMRS-SR-30. We then examined correlations between DMRS-SR-30 subscales and three symptom measures, as a test of convergent discriminant validity.

RESULTS

Table 2 shows the internal consistency for the DMRS-SR-30 subscales of ODF and defense levels. As expected, Cronbach's alpha values were higher for ODF (alpha = .890) and high adaptive (alpha = .703), and neurotic (alpha = .634) level scales, which consist of 30, eight and five items respectively. The values of alpha were generally lower for those defense levels consisting of four items or fewer. Similarly, defensive categories showed higher internal consistency (ranging from alpha = .817 to alpha = .580) than defense levels (ranging from alpha = .703 to alpha = .360), as they also have five or more items each.

Table 3 displays the descriptive statistics for ODF, defensive categories and defense levels rated with DMRS, DMRS-Q and DMRS-SR-30. ODF on all three measures was equal or near 5.00, which is generally the demarcation between neurotic and immature categories. All three values were within a third of a standard deviation from one another. From most to least prevalent, the order of the categories was the same: mature, immature, then neurotic for all three measures. Similarly the order of the prevalences was fully the same for all seven defenses levels for the DMRS and the DMRS-Q (r_s= 1.000; p<.001), and nearly the same for the DMRS-SR-30 (r_s = .964; p= .005).

Tables 4 and 5 display the correlations between DMRS-SR-30 and the observer-rated DMRS and DMRS-Q for the defense levels and categories. All the DMRS-SR-30 defense levels (**Table 4**) correlated positively with the corresponding subscales on DMRS and DMRS-Q. The correlations between the DMRS-SR-30 and the DMRS criterion measure were consistently higher than those with the DMRS-Q concurrent measure. Furthermore, the correlations between the DMRS-SR-30 and the DMRS on the diagonal were consistently higher than the off-diagonal correlations. For the correlations between the DMRS-SR-30 and DMRS-Q concurrent measure this was true for 6 scales, except the correlations were similar for both High Adaptive and ODF.

High correlations were obtained for ODF with both DMRS (*r*=.726; *p*<.001) and DMRS-Q (*r*=.626 *p*<.001). The correlations with the DMRS were generally high (ranging from *r*=.770 to *r*=.594; all *p-values*<.001) and slightly lower with the DMRS-Q (ranging from *r*=.575 to *r*=.419; all *p-values*<.001), except for minor image-distorting defenses that had a smaller correlation (r = .270, p<001) with the corresponding DMRS-Q scale. In **Table 5** The DMRS-SR-30 high adaptive defense category

TABLE 2 | Internal consistency and interrater reliability of the 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30).

	Cronbach's Alpha	N item
ODF	.890	30
Defensive Categories		
Mature	.703	8
Neurotic	.685	8
Immature	.817	14
Depressive	.757	9
Other Immature	.580	5
Defense Levels		
High Adaptive	.703	8
Obsessional	.360	3
Neurotic	.634	5
Minor image distorting	.520	3
Disavowal	.578	4
Major image distorting	.493	3
Action	.461	4
Median	.629	

TABLE 3 | Descriptive statistics among the three Defense Mechanism Rating Scales (DMRS) systems.

	DMRS		DMRS-Q		DMRS-SR-30	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
ODF	5.00	0.37	5.10	0.35	4.91	0.44
Defensive Categories						
Mature	38.17	8.84	40.35	9.85	39.42	10.08
Neurotic	23.02	5.79	22.83	6.70	20.22	5.73
Immature	38.76	8.54	36.80	7.11	38.69	9.18
Depressive	19.23	7.79	19.63	6.30	22.71	7.13
Other Immature	19.53	6.03	17.17	5.04	15.99	4.52
Defense Levels						
High adaptive	38.17	8.84	40.35	9.85	39.42	10.08
Obsessional	10.50	3.95	11.15	4.93	9.07	3.72
Neurotic	12.57	3.80	11.68	3.25	11.15	4.20
Minor image distorting	10.51	4.28	11.25	4.33	9.45	4.42
Disavowal	15.08	4.39	12.42	3.94	14.77	4.53
Major image distorting	6.57	3.26	6.44	3.07	8.36	3.92
Action	6.60	3.70	6.69	3.17	6.11	3.37

Mean scores and standard deviations are expressed as percentage score.

TABLE 4 | Correlations between the 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30) and the DMRS (criterion measure) and the DMRS-Q (concurrent measure) for overall defensive functioning (ODF) and defense levels.

		DMRS-SR-30							
		ODF	**High adaptive**	**Obsessional**	**Neurotic**	**Minor I-D**	**Disavowal**	**Major I-D**	**Action**
ODF									
	DMRS	**.726****	.658**	.128	−.172	−.187	−.384**	−.502**	−.497**
	DMRS-Q	**.626****	.560**	.108	−.127	−.208*	−.242*	−.456**	−.431**
High adaptive									
	DMRS	.640**	**.709****	−.117	−.349**	−.182	−.353**	−.406**	−.319**
	DMRS-Q	.514**	**.553****	−.110	−.239*	−.124	−.253*	−.320**	−.307**
Obsessional									
	DMRS	.032	−.202*	**.657****	.169	−.097	.006	−.057	−.134
	DMRS-Q	.061	.078	**.457****	−.090	−.054	−.001	.160	.107
Neurotic									
	DMRS	−.173	−.278*	−.021	**.770****	−.219*	−.032	.092	−.001
	DMRS-Q	−.125	−.186	−.004	**.575****	−.296*	.005	.092	.041
Minor image distorting									
	DMRS	−.181	−.197	−.069	−.173	**.638****	−.051	.050	.070
	DMRS-Q	.012	−.013	.075	−.161	**.270****	−.071	.073	.073
Disavowal									
	DMRS	−.235*	−.243*	−.023	−.058	−.010	**.630****	.018	.043
	DMRS-Q	−362**	−.324**	−.122	−.052	.187	**.419****	.113	.113
Major image distorting									
	DMRS	−.500**	−.449**	−.069	.274*	−.035	.012	**.699****	.204*
	DMRS-Q	−.406**	−.323**	−.107	.160	−.071	.039	**.502****	.274**
Action									
	DMRS	−.459**	−.281*	−.234*	−.108	.068	.168	.214*	**.594****
	DMRS-Q	−.510**	−.387**	−.209*	.038	.188	.101	.349**	**.471****

*p < .05; **p < .001.

TABLE 5 | Correlations between the 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30) and the DMRS (criterion measure) and the DMRS-Q (concurrent measure) for defensive categories.

Defensive Categories	**DMRS-SR-30**				
	Mature	**Neurotic**	**Immature**	**Depressive**	**Other Immature**
Mature					
DMRS	**.726****	−.301*	−521**	−.423**	−.203**
DMRS-Q	**.626****	−.280*	−.498**	−.501**	−.085
Neurotic					
DMRS	−.349**	**.729****	−.082	−.012	−.131
DMRS-Q	−.270*	**.519****	−.117	.139	−.092
Immature					
DMRS	−.554**	−.126	**.621****	.470**	.304**
DMRS-Q	−.435**	−.017	**.617****	.462**	.150
Depressive					
DMRS	−.514**	−.102	.620**	**.603****	.095
DMRS-Q	−.468**	−.017	−.665**	**.591****	−.011
Other Immature					
DMRS	−.341*	−.096	.283*	.002	**.468****
DMRS-Q	−.145	−.007	.240*	.006	**.323***

*p < .05; **p < .001.

correlated negatively with all lower level defense categories, with the immature category of greater magnitude than the neurotic category. Similarly, defensive categories showed high to moderate correlation levels with DMRS counterpart (ranging from *r*=.729 to *r*=.468; all *p-values*<.001) and moderate correlations with DMRS-Q (ranging from *r*=.626 to *r*=.519; all *p-values*<.001 except for other immature defenses that had weak correlation with the corresponding DMRS-Q scale (*r*=.323; *p*=.002). Finally, within the immature category, the correlations between the DMRS-SR-30 and the other measures were of greater magnitude for the depressive compared to nondepressive defenses.

Table 6 displays the correlations between DMRS-SR-30 and outcome measures of psychological distress (GSI), depression (BDI), and post-traumatic symptoms (IES-R). Correlations between DMRS-SR-30 and both BDI and IES-R were calculated

TABLE 6 | Convergent validity calculated as correlations between 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30) subscales and psychological distress measures.

	GSI(*N* = 67)	**BDI(*N* = 93)**	**IES-R(*N* = 93)**
ODF	**−.456****	**−540****	**−.402****
Defensive Categories			
Mature	**−.459****	**-522****	**-.367****
Neurotic	−.026	**.228***	.187
Immature	**.512****	**.421****	**.272***
Depressive	**.413****	**.475****	**.288***
Other Immature	**.329***	.105	.097
Defense Levels			
High adaptive	**−.459****	**−522****	**−.367****
Obsessional	.037	.009	−.104
Neurotic	.283	**.281***	**.326****
Minor image distorting	−.017	.036	−.131
Disavowal	.101	.124	.172
Major image distorting	**.391****	**.545****	**.475****
Action	.230	.234	.070

*p < .01; **p <. 001.

on 94 participants. Correlations between DMRS-SR-30 and GSI were calculated on 67 of the 94 participants who filled out the second questionnaire including all the 90 items of SCL-90. Demographic differences between participants that responded to the SCL-90 and participants that did not were calculated. We found no differences between groups in the prevalence of females (χ^2= .113; sig= .462), students ($\chi^{2\ =}$ 2.244; sig= .104), people living at parents' home (χ^2= .917; sig= .240), unmarried (χ^2= .882; sig= .253), and having children ($\chi^{2\ =}$ 1.334; sig= .197).

High negative correlations were found between DMRS-SR-30 ODF and all outcome measures, ranging from –.540 to –.402 (all *p-values*<.001) with the order of decreasing magnitude: BDI, GSI and IES-R. The high adaptive defense category had a similar order of correlations with the same three scales or slightly lower magnitude, also negative in direction. The immature defense category had the highest positive correlation figures with all symptom scales. Interestingly the sub-category of depressive defenses had the highest correlation with the BDI and lowest with IES-R. All of these correlations of the symptom measures with ODF are of smaller magnitude than the pair-wise correlations of ODF among the three defense measures themselves.

DISCUSSION

This study examined preliminary findings of reliability and validity of a novel self-report measure for the assessment of defense mechanisms based on the DMRS manual (42, 44). The DMRS-SR-30 (**Tables 7** and **8**) is the first self-report instrument measuring the whole hierarchy of defense mechanisms, considered a central feature of the theory of defense mechanisms (39–41). This initial study of the reliability and validity of the DMRS-SR-30 produced favorable results.

Examination of our first aim/hypothesis revealed the following about the internal consistency (reliability) of the defense summary scores of the DMRS-SR-30. We obtained excellent Chronbach alpha scores for the summary ODF score, which includes all 30 defense mechanism items. Defense categories and the defense levels with four or more items obtained good internal consistency, whereas the three levels (action, major-image-distorting and obsessional) with only three items each obtained only acceptable to low alpha scores. These findings may be influenced by the distribution of scores and sample size. Results from another study using the DMRS-SR-30 on a larger sample (N = 5,683) found that all alphas were above.613 (61), suggesting that the current smaller sample and its distribution of scores may have provided a limited test of reliability for some scales. Ongoing additional validation studies will provide further evidence of the internal consistency of the measure.

Our second aim examined the criterion and concurrent validity of the DMRS-SR-30 by comparing scores of this instrument to the DMRS and DMRS-Q on the same 94 subjects. We found excellent evidence of criterion validity with the DMRS. First the mean prevalence scores of the two instruments for the seven defense levels were highly similar, and the order of magnitudes from most to least were nearly the same (r_s= =.964; p= .005). Second, the table of correlations of the defense categories and levels indicates that the highest scores were always on the diagonal, of large magnitude (range:.599 to.770) and all highly significant. In particular, for ODF the two measures shared a substantial 50% of the variance. Finally, the off diagonal correlations were in predicted directions, with mature defenses of the DMRS-SR-30 negatively correlated with neurotic and immature categories and levels of the DMRS in line with the hierarchy of defenses.

The DMRS-Q offered a measure of concurrent validity. Everything that was noted above for the DMRS was also true for the relationships between the DMRS-SR-30 and the DMRS-Q, except that the magnitudes of the relationships were diminished somewhat, but still significant. The order of magnitude of the prevalence scores was the same found for the DMRS (r_s= = 1.00; p<.001) and the correlations on the diagonal for ODF and the defense categories (.327 to.626) and the defense levels (range:.270 to.575) were consistently lower than for the criterion comparison to the DMRS. Finally, the two measures shared 39% of the variance for the summary ODF score, a 22% lower number than the criterion comparison. In short the DMRS-SR-30 shows very good criterion validity and good concurrent validity (DMRS-Q), as well.

Our third aim was to examine evidence for convergent and discriminant validity of the DMRS-SR-30 which our **Table 6** provided. Research on defenses has found that ODF and specific parts of the defense hierarchy correlate with a variety of symptom measures, including anxiety, depression and general symptom levels (53, 54, 75, 76). We confirmed that the DMRS-SR-30 ODF and the mature defense level were negatively associated, in decreasing order of magnitude, with depressive symptoms (BDI), general distress (GSI) and post-traumatic stress symptoms (IES-R). The absolute magnitude of these associations (range: –.402 to –.540) was substantially less than the correlation of ODF with the criterion DMRS (.726). This demonstrates both convergent and discriminant validity: that DMRS-SR-30 ODF correlates with symptom measures as in other studies, but these correlations are lower than with its criterion. One limitation is that we did not include a measure known to correlate only slightly with defenses which would have further strengthened the discriminant finding. In line with research findings on the psychological effects of quarantining (27, 77, 78), we found ODF and outcome measures means fell in the neurotic range (61, 62), confirming results of a recent study that first applied the measure to a large sample of Italian people assessed during the first week of lockdown for COVID-19 pandemic (28).

We observed differential associations which further elucidate the convergent validity of specific defense categories of the DMRS-SR-30. First, mature defenses were negatively associated with neurotic and immature defense categories and with higher symptom levels across a variety of measures, as reported elsewhere for the DMRS (8). Secondly, within the immature defense category, the distinction between the depressive and

nondepressive defenses reflected differential relationships to symptoms. Both depressive and nondepressive defenses correlated with general distress (GSI); however, only depressive defenses correlated with depressive (BDI) and post-traumatic (IES-R) symptoms. Furthermore, the group of depressive defenses obtained its greatest correlation with depressive symptoms, in line with other theoretical and empirical findings (56). This specific association of depressive defenses to depression is consistent with the putative, mediating role of change in depressive defenses and decreasing depressive symptoms over treatment of depressed individuals (56, 59). Finally, the four Neurotic level defenses (repression, dissociation, displacement, and reaction formation) indicated the strongest association to the IES-R, reflecting the likely contribution of these defenses to the anxiety and dissociative components of post-traumatic symptoms.

The present study has several important limitations. The small nonclinical sample size does not allow a complete examination of low base-rate subscales, may not have provided stable estimates in those cases, and may limit the generalizability of study findings. Moreover, the use of a convenience sample obtained through social media may not have yielded sufficient prevalence of individuals with psychiatric disorders, which, in turn, may affect the scale scores and the examination of convergent validity. Further studies on larger samples including both clinical and community participants should be done to check and cross-validate the accuracy of our findings. Despite sharing 50% of the variance (good criterion validity with the DMRS), the DMRS-SR-30 items tap only the aspect of defenses about which individuals can consciously report. Therefore, it is likely that there will be some clinical phenomena that self-report items do not capture as well as the original observer-rated criterion method. This possibility will require empirical documentation. The DMRS-SR-30 has a limited number of items which makes it impossible to examine the reliability of single item defenses, and difficult to examine the validity of individual defenses and some defense levels, except in large samples, given low base rates of some defenses and levels. The limited number of items included in the DMRS-SR-30 did not allow us to investigate internal consistency on individual defenses subscales, most of which are single-item scales. This bias has been considered by the authors as the main rationale for developing a longer version of the DMRS-SR in the future.

Future studies should examine the degree to which the DMRS-SR-30 is useful in studies of psychopathology and treatment. While the DMRS-SR-30 showed good criterion validity, we do not yet know whether it will serve as a useful instrument to delineate dynamic factors useful for treatment assignment. Furthermore, examination of change in the measure over time with treatment may aid the study of change in defenses

TABLE 7 | The 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30) questionnaire (English version).

In the past week, how much did you deal with difficult emotions or situations in the following ways?				
Not at all (0)	**Rarely/slightly (1)**	**Sometimes/somewhat (2)**	**Often/a lot (3)**	**Very often/much (4)**
1) Did you perceive others as “all good” or “all bad”?				
2) Did you react as if you were detached from personally relevant issues?				
3) Did you develop somatic symptoms, such as headache, stomach pain, or the loss of ability to do something, in response to emotional situations?				
4) Did you offer physical or psychological help to others in need?				
5) Did you have repetitive or serial daydreams to which you retreated in lieu of real life?				
6) Did you think about how you would handle difficulties that you might expect in the future?				
7) Did you feel as if there was nothing positive or redeeming about yourself?				
8) Did you have an attitude of giving much more than you received without perceiving the imbalance?				
9) Did you ask for physical or emotional support while doing your best to handle the problem?				
10) Did you try to diffuse the tension by engaging in creative activities?				
11) Did you have an attitude of suspiciousness or perceive others as untrustworthy, unfaithful, or manipulative?				
12) Did you make humorous comments about challenging personal issues or stressful situations?				
13) Did you reflect upon your emotional experiences and personal thoughts?				
14) Did you try to take your anger out on yourself or express it with self-harming behaviors?				
15) Did you justify or give plausible explanations to cover up the real reasons for personal problems or stressful situations?				
16) Did you take an active role in solving problems that arose?				
17) Did you idealize yourself or others for your/their personal characteristics?				
18) Did you consciously or unconsciously try to irritate someone in indirect or annoying ways?				
19) Did you temporarily put aside your personal needs to deal with other things that needed to be done?				
20) Did you focus on minor or unrelated matters that distracted you away from a problem that makes you anxious?				
21) Did you discuss an emotional topic in general or impersonal way, without considering or experiencing your feelings?				
22) Did you complain about how others don’t understand you or don’t really care?				
23) Did you experience strong feelings toward someone, thinking that the other person intended to make you feel that way?				
24) Did you feel confused, “spaced out,” or unable to talk about a distressing topic?				
25) Did you engage in verbal or physical fights?				
26) Did you have trouble remembering simple things?				
27) Did you avoid thinking about personal problems or feelings?				
28) Did you perceive yourself as very strong, powerful, untouchable?				
29) Did you have contradictory or conflictual ideas about a topic that makes you anxious?				
30) Did you devalue yourself or others for your/their personal characteristics?				

TABLE 8 | The 30-item Defense Mechanism Rating Scales Self-Report (DMRS-SR-30) questionnaire (Italian version).

Nell'ultima settimana, quanto hai affrontato emozioni o situazioni difficili nei seguenti modi?				
Per niente (0)	**Raramente/poco (1)**	**A volte/abbastanza (2)**	**Spesso/molto (3)**	**Molto spesso/moltissimo (4)**
1) Hai percepito qualcuno come "tutto buono o tutto cattivo"?				
2) Hai reagito come se fossi distaccato rispetto a tematiche di rilievo personale?				
3) Hai sviluppato sintomi somatici, come mal di testa, mal di pancia, perdita di capacità nel fare qualcosa, in risposta a situazioni stressanti?				
4) Hai offerto sostegno fisico o psicologico a persone in difficoltà?				
5) Hai fatto sogni ad occhi aperti ripetitivi o ricorrenti nei quali ti sei ritirato al posto di affrontare la realtà?				
6) Hai pensato a come dovrai affrontare le difficoltà che ti aspetti nel futuro?				
7) Hai avuto una percezione di te stesso come se non c'è nulla di positivo o buono in te?				
8) Hai avuto la tendenza a dare molto più di quanto hai ricevuto senza percepire uno sbilanciamento?				
9) Hai chiesto sostegno fisico o psicologico facendo del tuo meglio per risolvere il problema?				
10) Hai cercato di scaricare la tensione attraverso l'impegno in attività creative?				
11) Hai avuto un atteggiamento sospettoso o hai percepito gli altri come inaffidabili, infedeli o manipolativi?				
12) Hai fatto commenti ironici su questioni personali difficili o situazioni?				
13) Hai riflettuto sulle tue idee ed esperienze emotive e pensieri personali?				
14) Hai cercato di sfogare la rabbia su te stesso o di esprimerla attraverso comportamenti autolesionistici?				
15) Hai giustificato o dato spiegazioni plausibili per coprire le reali ragioni di un problema personale o situazione stressante?				
16) Hai avuto un ruolo attivo nel risolvere problemi che sono emersi?				
17) Hai idealizzato te stesso o degli altri per le tue/loro qualità personali?				
18) Hai cercato consciamente o inconsciamente di irritare qualcuno in modo indiretto o fastidioso?				
19) Hai messo temporaneamente da parte i tuoi bisogni personali per far fronte ad altre cose che dovevano essere fatte?				
20) Hai focalizzato l'attenzione su questioni di minore o estranea rilevanza che ti hanno distratto da un problema che ti genera ansia?				
21) Hai discusso un argomento emotivo in modo generale e impersonale, senza considerare o sentire le tue emozioni?				
22) Ti sei lamentato di come gli altri non ti capiscano o non si preoccupino per te?				
23) Hai provato forti sentimenti verso qualcuno pensando che l'altra persona abbia voluto farti sentire proprio in quel modo?				
24) Hai avuto percezione di sentirti confuso, "sballato," incapace di parlare di argomenti dolorosi?				
25) Hai preso parte a scontri verbali o fisici?				
26) Hai avuto difficoltà a ricordare cose semplici?				
27) Hai evitato di pensare a problemi personali o alle tue emozioni?				
28) Hai avuto la percezione di te come molto forte, potente o intoccabile?				
29) Hai avuto idee contrastanti e conflittuali su un tema che genera ansia?				
30) Hai svalutato te stesso o gli altri per le tue/loro qualità personali?				

as potential mediators of change in psychopathology, such as depression. The ease of the self-report format should facilitate studies of this sort.

CONCLUSION

Assessing defense mechanisms is an important part of the diagnostic process of both physical and mental disorders (59, 79–83). Improvement in the adaptiveness of defense mechanisms during psychotherapy was associated with greater adjustment and positive outcome (8, 47, 64, 84). Recent findings demonstrated that defense mechanisms had relevant impact on resilience of community sample to stressful life event as quarantining for COVID-19 pandemic (28, 61). The DMRS-SR-30 is the first self-report questionnaire assessing the whole hierarchy of defense mechanisms as described by the DMRS gold-standard theory (39–42). The Italian version of the DMRS-SR-30 has proven to have acceptable reliability and good criterion and concurrent validity, as well as acceptable convergent and discriminant validity. Further studies on larger and multicultural samples are needed to confirm these preliminary findings and to test other psychometric properties of the measure.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Pisa. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG and JP conceived the measure and contributed to the data analysis. ML, MM, SV, AP, MF, and SM contributed to data collection and assessment. MG and CC drafted the first version of the manuscript. JP extensively revised the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Psychology

SYSTEMATIC REVIEW
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The Relationship Between Alexithymia and Type 2 Diabetes: A Systematic Review

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Background: This systematic review analyzed the relationship between alexithymia, considered as the inability to recognize and express thoughts and emotions, and type 2 diabetes mellitus (T2DM), one of the most common chronic illness, characterized by a metabolic disorder burdened by high morbidity and mortality worldwide due to its outcomes.

Methods: PRISMA guidelines were followed throughout this systematic review of the recent literature indexed in the databases PubMed, PsycInfo, Scopus, and Web of Science. Search terms for eligible studies were: "Type 2 diabetes" OR "T2DM" AND "Toronto Alexithymia Scale" OR "TAS-20"[All Fields].

Results: The initial search identified 61 indexed scientific publications. After screening we found that seven publications met the established scientific inclusion and exclusion criteria. It emerged that alexithymic patients ranged from 25 to 50% across the examined publications and it appeared that patients with T2DM generally reflected greater values of alexithymia, revealing particular differences among TAS domains. Moreover, emlpoyed participants were alexithymic to a greater extent compared to non-working participants (77.8 vs. 35.4%) and alexithymia was 2.63 times more severe among working participants when examining predictors of alexithymia. When evaluating the correlations between alexithymia and HbA1c or fasting blood glucose levels we found strong associations equal to 0.75 and 0.77 for TAS-20 total scores, respectively. While alexithymic participants showed significantly higher levels of HbA1c and blood glucose when compared to the non-alexithymic participants.

Conclusions: The results of this systematic review of the current literature highlight the need of alexithymia evaluation in patients with T2DM. The high prevalence in T2DM and strong associations with poorly regulated diabetes and psychological distress, indicate a significant relationship between poor glycemic control and psychological distress, such as anxiety and depression, and quality of life. Further studies are needed focusing on age and gender differences in order to be able to improve clinical psychological care and prevention.

Keywords: alexithymia, psychological distress, type 2 diabetes mellitus, metabolic syndrome, chronic disease

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INTRODUCTION

Alexithymia is considered as the inability to distinguish between emotions, thoughts, and physiological responses to stimuli, involving difficulties in recognizing and verbalizing emotions and externally oriented thinking (Nemiah and Sifneos, 1970; Sifneos, 1996; Taylor and Bagby, 2000; Tordeurs and Janne, 2000). Alexithymia is also defined as a personality trait which manifests itself in comorbidity with different physical and psychopathological disorders (Lumley et al., 2005, 2007; Mattila et al., 2009; Honkalampi et al., 2010; Tolmunen et al., 2011; Marchetti et al., 2019) and retained as a transient variable state related to both psychopathological conditions and stress levels (Pollatos et al., 2011). Also, alexithymia seems to be involved in the pathogenetic mechanism of several somatic illness (Porcelli et al., 1996; Willemsen et al., 2008; Mazaheri et al., 2012; Talamonti et al., 2016; Marchi et al., 2019; Martino et al., 2020c) and it appears to be associated with depression and anxiety in patients with type 2 diabetes (T2DM) (Friedman et al., 2003; Luminet et al., 2006; Pouwer et al., 2010; Sapozhnikova et al., 2012; Shinkov et al., 2018). Alexithymia and psychological distress, as anxiety and depression, may impair patient's compliance and adherence, concurring in a worst clinical presentation and course of a chronic disease (Sapozhnikova et al., 2012; Hintistan et al., 2013; Mnif et al., 2014; Stanton and Hoyt, 2017; Marchini et al., 2018; Settineri et al., 2019; Vicario and Martino, 2020; Vicario et al., 2020; Vita et al., 2020).

T2DM is a common chronic illness and it is considered a major health concern due to its prevalence and outcomes. T2DM may involve a serious impact on both morbidity and mortality, compromising individuals' health and perceived quality of life and provoking a very thoughtful social burden to society (Perry et al., 2015; Craparo et al., 2016; Catalano et al., 2019; Conversano, 2019; Di Giuseppe et al., 2019, 2020; Martino et al., 2019c, 2020b; Merlo, 2019; Zimmerman et al., 2019; Lenzo et al., 2020). T2DM is a pandemic chronic metabolic disease, due to insulin deficit and resistance, which affects more than 280 million people worldwide and within the next decade it is expected that more than 430 million people will suffer T2DM (American Diabetes Association, 2018).

T2DM is a chronic disease with severe complications if poorly controlled and could in turn compromise psychological balance (Whithorth et al., 2016). It is hypothesized that low glycemic control affects brain and mental functions leading to psychological distress, which is shown to be more prevalent in T2DM patients than in the general population (Lustman and Clouse, 2005; Bahar et al., 2006; Collins et al., 2009; Lee et al., 2009; Papelbaum et al., 2010; Sulaiman et al., 2010), as even results by the increased risk of mental disorders (Anderson et al., 2001; Collins et al., 2009; Lemche et al., 2014). Particularly, some studies revealed that compliance and adherence are crucial factors to adequately manage such chronic disease (Marchini et al., 2018; Martino et al., 2019b).

It is well-known that poor metabolic control in T2DM leads to several severe and life threatening complications as among other cardiovascular diseases (Li et al., 2008; American Diabetes Association, 2018; Guicciardi et al., 2019). However, poor metabolic control is also associated with increased risk of psychopathological conditions, including also alexithymia (Abramson et al., 1991; Luminet et al., 2006).

Focusing the opposite way, patients suffering from alexithymia and T2DM have a significant metabolic imbalance and control, which might be explained by difficulty in recognizing their body signals, perceptions, and emotions (Abramson et al., 1991; Sapozhnikova et al., 2012; Hintistan et al., 2013; Lemche et al., 2014; Luca et al., 2015; Rosa et al., 2019; Orrù et al., 2020). Moreover, the failure to recognize body symptoms and emotion perceptions could lead to a further incomprehensible psychological and physical suffering, due to poorly regulated T2DM, which may impair the ability to manage their diabetes (Friedman et al., 2003).

Thus, it is crucial to both elaborate and plan a deep clinical psychological investigation together with adequate medical evaluation in order to find psychological features, such as alexithymic patients, in favor of the best health course and specific treatments. Therefore, the aim of this systematic review is providing the current insights on the alexithymic characteristics of patients with T2DM and highlighting the clinical faces of this complex. Our goal is to improve knowledge on the complex of alexithymia, T2DM and other related factors, which may support both psychologist and physicians to realize strategies and interventions to promote the adequate managing of T2DM. Better understanding of this complex among patients and health care professionals, might improve patients' knowledge of such chronic illness, way of feeling themselves and perceived quality of life.

MATERIALS AND METHODS

Data Source and Search Strategy

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009; Moher et al., 2009). PubMed, PsycInfo, Scopus, and Web of Science databases were searched in March 2020 for eligible studies between 2015 and 2020, and the following combination of search terms was employed: "Type 2 diabetes*" OR "T2DM" AND "TAS-20" OR "Toronto Alexithymia Scale" [All Fields]. The term TAS-20 (or Toronto Alexithymia Scale) was selected to search records providing empirical data about alexithymia, by relying on the most used assessment instrument.

Publication Screening and Eligibility Criteria

After conducting the first screening we eliminated study duplicates. During the second selection all titles and abstracts were screened and possible relevant studies were identified for full text review by two independent researchers in clinical psychology for eligibility. Inclusion criteria were: Scientific publications in English and with peer review published from 2015 and up to March 2020, adopting quantitative research designs, and reporting relevant and empirical data on alexithymia

and T2DM. The limited time range (from 2015 to 2020) was selected because the authors' choice was to review updated literature providing results from very recent publications.

Analysis Reviewed Publications and Data Synthesis

Methods were performed accordingly to the PRISMA guidelines (Liberati et al., 2009; Moher et al., 2009), considering that the heterogeneity of the explored research designs was not appropriate to be explored by a meta-analysis. To avoid the risk of bias, researchers in clinical psychology reviewed independently the articles to determine the adequate reliability of the used methodology. Data were extracted into an Excel spreadsheet, with bibliographic information and study specific details were recorded, such as sample characteristics (e.g., age, gender, sample size, presence of comparison groups) and scores of TAS-20 and further used measures. Selected studies were considered by comparing significant data and identifying the indexes of the measured variables, to provide a qualitative synthesis. Discrepancies on inclusion/exclusion criteria and study characteristics were solved by consensus.

RESULTS

Search Result

Figure 1 shows our search result and screening results according to PRISMA. Our search identified 61 publications. Seventeen publications were duplicates leaving our search with 44 publications for title and abstract review. After this review process we identified in total 11 papers for full review. The excluded publications did not fulfill the inclusion criteria as 23 did not address T2DM, one did not address alexithymia and nine did not address any of the two. Thus, the remaining 11 publications were full text reviewed and four of them were removed for the following reasons: one did not provide English full-text (Shayeghian et al., 2015), one did not provide empirical data (Melin et al., 2016), and two were more widely addressed to patients with diabetes without providing specific or disaggregated results about patients with T2DM (De Oliveira Regina and Tambascia, 2017 Marchini et al., 2018). We concluded that seven papers could be included in our systemic review based on the inclusion criteria.

Study Characteristics

We found that most included studies were conducted in Italy (three out of seven), and pertained to cross-sectional research studies. Specifically, four studies adopted a one-sample research design (Luca et al., 2015; Avci and Kelleci, 2016; Lai et al., 2019; Martino et al., 2019a), whereas three studies also included comparison groups referring to healthy controls (Shahi and Mohammadyfar, 2017; Fares et al., 2019) or patients with T1DM (Melin et al., 2017). Five studies reported specific inclusion/exclusion criteria for patient selection (Avci and Kelleci, 2016; Melin et al., 2017; Fares et al., 2019; Lai et al., 2019; Martino et al., 2019a). The most reported inclusion criterion was having good language proficiency to fully comprehend or perform the psychological administration (Melin et al., 2017; Fares et al., 2019; Lai et al., 2019; Martino et al., 2019a). Three studies also reported time since diagnosis as a further criterion, including patients with a diagnosis since at least 6 months (Avci and Kelleci, 2016), 1 year (Lai et al., 2019), or 5 years (Martino et al., 2019a). Whereas, the most frequent exclusion criterion was lack of cognitive or psychiatric disorders (Avci and Kelleci, 2016; Melin et al., 2017; Fares et al., 2019; Lai et al., 2019; Martino et al., 2019a). Concerning sample size, the retrieved studies included a number of patients with T2DM ranging from 24 (Melin et al., 2017) to 326 (Avci and Kelleci, 2016), with an average of 108 patients ($SD = 102$). Overall, the patients were aged 27–90 years (mean age 63 years). Gender was fairly well-distributed in the considered studies, with a mean of 53% of male patients (average of 36.2–68.7% in the studies). Three studies (Luca et al., 2015; Fares et al., 2019; Lai et al., 2019) reported patient diabetes duration which in general was above 10 years. Besides, patients' diabetes complications were reported in three studies (Avci and Kelleci, 2016; Fares et al., 2019; Martino et al., 2019a) and diabetes-related treatment information was provided in more than half (Luca et al., 2015; Avci and Kelleci, 2016; Melin et al., 2017; Fares et al., 2019). The main characteristics of the studies are reported in **Table 1**.

The Prevalence of Alexithymia in Patients With Type 2 Diabetes Mellitus

With the exception of two of the seven studies (Shahi and Mohammadyfar, 2017; Lai et al., 2019), information about the TAS-20 total score was provided. The mean value of alexithymia ranged from 52.2 (Fares et al., 2019) to 60.5 (Martino et al., 2019a), thus falling in the range of intermediate/borderline alexithymia, which is comprised between 52 and 60 points. In four studies, the percentage of alexithymic patients ($\geq$61) was also indicated (Luca et al., 2015; Avci and Kelleci, 2016; Melin et al., 2017; Fares et al., 2019), ranging from 25% (Melin et al., 2017) to 50% out of the total sample (Luca et al., 2015). Finally, three studies compared alexithymia of patients with T2DM with healthy controls (Shahi and Mohammadyfar, 2017; Fares et al., 2019) or patients with T1DM (Melin et al., 2017) and showed statistically significant differences, with patients with T2DM generally having greater TAS-20 values of alexithymia or likelihood to be alexithymic based on the accepted cutoff.

Concerning the three subscales of TAS-20 (Difficulty Identifying Feelings, Difficulty Describing Feelings, Externally-Oriented Thinking), we calculated effect sizes (ES) (expressed as the mean divided by the standard deviation of the sample) for each study providing descriptive statistics of the alexithymia dimensions (Luca et al., 2015; Avci and Kelleci, 2016; Shahi and Mohammadyfar, 2017; Fares et al., 2019; Martino et al., 2019a). This was to compare the mean values on the different subscales. On average, patients scored higher on Externally-Oriented Thinking (ES = 5.04) compared to both Difficulty Describing Feelings (ES = 4.10) and Difficulty Identifying Feelings (ES = 3.20), with the latter having the lowest mean values.

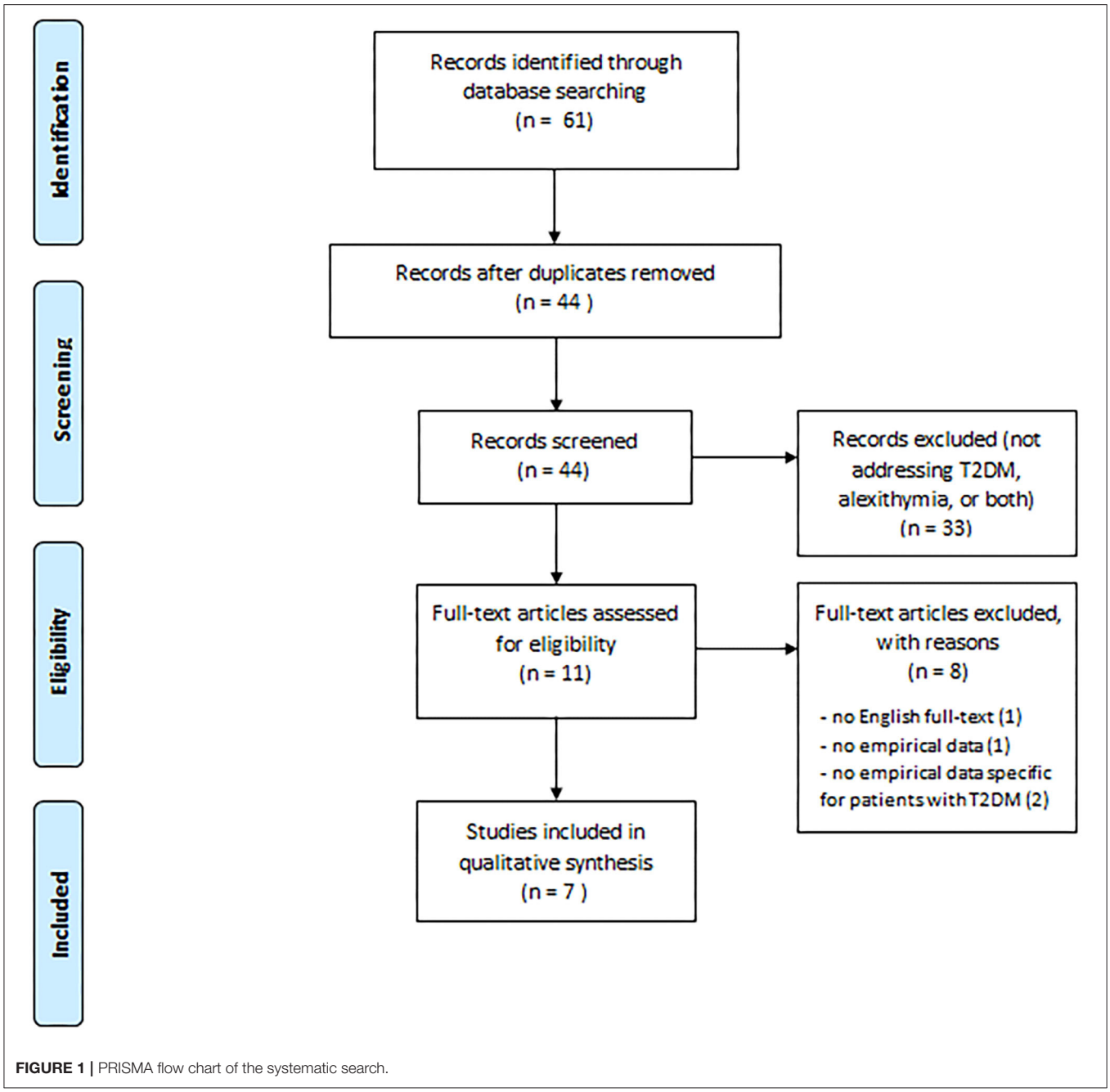

FIGURE 1 | PRISMA flow chart of the systematic search.

Alexithymia and Socio-Demographic Characteristics

Two studies specifically evaluated gender differences in patients with T2DM. Particularly, Avci and Kelleci (2016) found alexithymia was more severe in females compared to male participants (45.6% of females were alexithymic vs. 29% of males). As well, multivariate analysis of factors affecting alexithymia did not confirm gender as a statistically significant predictor. Conversely, Fares et al. (2019) showed male participants were more likely to present alexithymia than females (46.0 vs. 19.5%, respectively), although multivariate analysis of alexithymia predictive factors revealed that gender did not show significant.

With regard to age differences, two publications showed no statistically significant differences based on either the patients alexithymic status (Luca et al., 2015; Avci and Kelleci, 2016) or the inspection of potential predictors of alexithymia (Avci and Kelleci, 2016).

The study by Avci and Kelleci (2016) examined further socio-demographic information in relation to alexithymia, such as participants' education level, marital status, employment status, and perceived income level. In general, the publications showed

TABLE 1 | Included items characteristics.

Authors	Year	Journal	Country	Purpose	Number of patients with T2DM (% males)	Age range or mean age (SD)	Presence of comparison groups and sample size
Fares et al.	2019	Journal of Diabetes and Metabolic Disorders	Lebanon	Evaluate the prevalence of alexithymia and its relationship with glycemic control among Lebanese adults with T2DM compared to healthy controls	104 (60.6%)	29–90 years; 59.4 (14.2)	Yes (100 healthy controls)
Lai et al.	2019	European Review for Medical and Pharmacological Sciences	Italy	Assess the association among alexithymia, anxiety, depression, stress, and social support with adherence and healthcare spending in type 2 diabetic patients	64 (68.7%)	55–90 years; 67 (11)	No
Martino et al.	2019	Mediterranean Journal of Clinical Psychology	Italy	Investigate the relationship between alexithymia and affective dimension such as anxiety and depression levels, and health related quality of life in patients with T2DM	47 (36.2%)	55–75 years; 65.3 (5.9)	No
Melin et al.	2017	BMC Psychiatry	Sweden	Compare the clinical presentation of patients with T1DM and T2DM in relation to self-reported depression, anxiety, alexithymia, obesity, and midnight salivary cortisol (MSC)	24 (50%)	31–59 years	Yes (148 patients with T1DM)
Avci and Kelleci	2016	Patient Preference and Adherence	Turkey	Determine the prevalence of alexithymia in patients with T2DM and the factors affecting it, such as anxiety and depression	326 (47.5%)	62.0% were in the ≥65 years age group	No
Shahi and Mohammadyfar	2016	Personality and Individual Differences	Iran	Compare depression, anxiety, stress, quality of life, and alexithymia in people with T2DM and their non-diabetic counterparts	60 (50%)	57.8 (10.5)	Yes (60 healthy controls)
Luca et al.	2015	Journal of Endocrinological Investigation	Italy	Assess the prevalence of depression and alexithymia among patients with T2DM and investigate the possible correlations between these psychopathological phenomena and glycemic control	128 (58.6%)	64.8 (11.2)	No

that working participants were alexithymic to a greater extent than unemployed ones (77.8 vs. 35.4%) and alexithymia was 2.63 times more severe among employed participants when examining alexithymia predictors, whereas no relations were found on other considered socio-demographic variables.

Alexithymia and Lifestyle

Two studies inspected the relationship between alexithymia and lifestyle factors. Specifically, the study by Fares et al. (2019) found that patients with alexithymia had higher frequencies of alcohol consumption (75.7 vs. 37.3%), lower rates of physical activity (27 vs. 50.7%), and fewer self-reports of adequate dietary intake related to diabetes (40.5 vs. 71.6%). Whereas, no significant association with tobacco and body mass index (BMI) was observed. However, such factors did not constitute significant predictors of alexithymia in multivariate analysis. Furthermore, the study by Lai et al. (2019) observed that TAS-20 difficulties in identifying and describing feelings were negatively associated with physical activity with low effect sizes ($r = -0.26$ and $r = -0.25$, respectively).

Alexithymia, Diabetes Duration, and Treatment Information

Two studies examined the relationship between alexithymia and diabetes duration. Avci and Kelleci (2016) found a greater rate of alexithymia among patients who had diabetes ≥11 years, but diabetes duration was not a reliable predictor of alexithymia. On the other hand, the study by Luca et al. (2015) showed that alexithymic patients had, on average, longer diabetes duration (13.5 vs. 10.3 years) despite not to a statistically significant extent.

The association of alexithymia and treatment-related variables was also considered. Avci and Kelleci (2016) did not find

differences between alexithymic and non-alexithymic patients based on type of treatment (insulin + diet vs. oral antidiabetic + diet), which did not result in a significant predictive factor of alexithymia. Consistently, the study by Luca et al. (2015) did not show differences in diabetes treatment (diet, per oral anti-diabetics, or subcutaneous insulin) based on patients' alexithymic status.

Alexithymia, Glycemic Control, and Hospitalization

Three studies examined the potential association between alexithymia and glycemic control. The study by Fares et al. (2019) assessed the impact of alexithymia on glycemic control based on values of HbA1c and fasting blood glucose levels. Correlations of alexithymia with HbA1c and fasting blood glucose levels showed a strong association equal to 0.75 and 0.77 for TAS-20 total scores, respectively (and ranging from 0.63 to 0.75 and from 0.67 to 0.77 at the relative subscales). Besides, alexithymic patients showed significantly higher levels of HbA1c and blood glucose levels as compared to not-alexithymic patients; specifically, those having HbA1c >7% were more likely to have alexithymia in comparison to their counterparts. The study by Avci and Kelleci (2016) confirmed a high correlation between alexithymia and HbA1c (equal to 0.81) and a greater rate of alexithymic patients among those having HbA1c levels ≥7% (44 vs. 26.9% of those with normal values of glycemic control). Then, alexithymia was found 2.09 times higher among patients with HbA1c ≥7.0% compared to their counterparts. The study by Luca et al. (2015) detected a statistically significant but modest correlation ($r = 0.30$) between HbA1c and TAS-20 factor about identifying feelings. HbA1c was observed higher in alexithymic patients compared to non-alexithymic ones. Further, patients with pathological high HbA1c had higher TAS-20 and subscale scores compared to patients with HbA1c within normal range.

Besides this, hospitalization due to acute and chronic diabetes complications was considered by two studies. Lai et al. (2019) showed that TAS-20 total and externally oriented thinking scores were positively correlated with the number of hospitalization days and that alexithymia was predictive of a substantial increase in hospitalization. In line with this, the study by Fares et al. (2019) found that patients with alexithymia had hospitalizations for hyperglycemia (during the past year) ∼5 times more frequent than their counterparts (82.9 vs. 17.1%) and that hospitalization represented a significant predictor of alexithymic status.

Alexithymia and Psychological Distress

Alexithymia and Depression

The association with alexithymia and further variables regarding the psychological status were evaluated. Four studies considered depression levels (Luca et al., 2015; Avci and Kelleci, 2016; Melin et al., 2017; Martino et al., 2019a). Avci and Kelleci (2016) used the depression subscale of the Hospital Anxiety and Depression Scale (HADS), using the cutoff point ≥8 to determine the risk of depression. A very high correlation emerged between alexithymia and depression levels ($r = 0.80$). Comparing alexithymic and non-alexithymic patients, the authors found a higher rate of participants with clinically significant depression (51.7 vs. 26.3% of participants whose depression subscale score was <8). In more detail, according to the multivariate analysis, alexithymia was 2.57 times more severe in the depressed participants than in their counterparts. The study by Luca et al. (2015) used the Hamilton rating scale for depression (HAM-D) investigating the presence of depressive symptoms, with a score >7 indicating the presence of a depressive condition. Overall, alexithymic patients presented significantly higher depression levels than non-alexithymic patients, both regarding the total score and most of HAM-D subscale scores (i.e., anxiety/somatization, cognitive disturbance, diurnal variation, psychomotor retardation, and sleep). Also, TAS-20 total and subscale scores were higher in depressed patients than in non-depressed patients. Melin et al. (2017) assessed self-reported depression through the relative subscale of the HADS adopting the recommended cut off level ≥8 points. They highlighted that depressed patients had higher prevalence of alexithymia compared to non-depressed patients (67 vs. 11%) and that being alexithymic was a predictive factor for depression risk. Then, Martino et al. (2019a) administered the Beck Depression Inventory-second edition (BDI-II) to evaluate depression levels, which correlated with the TAS-20 total score, to a moderate extent ($r = 0.33$).

Alexithymia and Anxiety

Two studies out of the seven assessed publications found association between alexithymia and anxiety. The study by Avci and Kelleci (2016) used the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), adopting the cutoff point of 11 to determine clinically significant anxiety levels. A high association was detected between alexithymia and anxiety ($r = 0.65$) and a greater rate of patients with anxiety problems was found in alexithymic rather than non-alexithymic patients (61.3 vs. 38.7%). In addition, the results of multivariate analysis showed that alexithymia was 3.77 times more severe in patients whose anxiety score was ≥11. Whereas, the study by Martino et al. (2019a) used the Hamilton Anxiety Rating Scale (HAM-A) to detect anxiety levels, allowing the measurement of two components respectively regarding psychic and somatic anxiety. Strong statistically significant associations were detected between alexithymia and anxiety ($r = 0.66$), both the psychic ($r = 0.56$) and somatic components ($r = 0.61$). With reference to the alexithymia factors, difficulty identifying feelings was strongly associated with overall anxiety levels ($r = 0.57$), regarding both psychic ($r = 0.33$), and somatic anxiety ($r = 0.57$). Moreover, difficulty describing feelings was associated only with HAM-A total score to a moderate extent ($r = 0.37$), whereas no association was found with externally-oriented thinking.

Alexithymia and Quality of Life

Two studies focused association between alexithymia and quality of life. Luca et al. (2015) evaluated the quality of life using the Quality of Life Index (QL), as an overall measure pertaining to activity, daily life, health, support, and mood. The authors found that quality of life was lower in alexithymic patients than in non-alexithymic patients. Whereas, the study by Martino et al. (2019a), evaluated perceived health-related quality of life using the Short Form Health Survey (SF-36) questionnaire, which provided two indexes regarding physical and mental well-being (*PCS*, physical component summary and *MCS*, mental

component summary, respectively). Their findings highlighted that alexithymia was negatively associated with the MCS value to a moderate extent ($r = -0.41$), specifically only with difficulty identifying feelings ($r = -0.50$), while no association was found with the PCS value.

DISCUSSION

Our study aim was to evaluate the current evidence of T2DM in relation to alexithymia. A limited number of scientific publications are focusing emotional capacities among patients with T2DM, despite the relevance of emotion-management in such chronic disease being a well-acknowledged problem in terms of treatment adherence and health status (Cummings et al., 2014; Gonzalez et al., 2015).

With regard to the prevalence of alexithymia, our findings suggest patients with T2DM show values reflecting possible alexithymic traits. Specifically, among patients with T2DM, it is estimated that those being alexithymic (based on the accepted cutoff for TAS-20) may range from 25 to 50%. The significant prevalence of alexithymia in this specific population is further confirmed by studies using comparison groups composed of healthy controls (Shahi and Mohammadyfar, 2017; Fares et al., 2019) or patients with T1DM Melin et al. (2017). In more detail, among the alexithymia factors, it is worth-noting that externally-oriented thinking shows the highest values. Differently from difficulties identifying or describing feelings, this dimension represents a rigid and concrete cognitive style of thinking which does not necessarily include the emotional experience. It reflects the tendency to focus on external events over inner experiences resulting in poor resources of introspection. From a psychosomatic perspective, along with a limited fantasy life, it relates to the operative thinking observed in patients with physical illnesses (Marty and De M'Uzan, 1963). Besides, it is associated with lower level of body attention, less time spent to body scan, less bodily perceived change, and lower reflexion (Fantini-Hauwel, 2014), thus suggesting the potential enactment of avoidant strategies, in psychodynamic terms (Marchetti et al., 2017; Marchini et al., 2018; Fantinelli et al., 2019; Velotti et al., 2019).

About the relationship between alexithymia and socio-demographic characteristics, the evaluated scientific publications show contrasting observations with regard to gender differences (Avci and Kelleci, 2016; Fares et al., 2019) and no statistically significant results due to the participants' age (Luca et al., 2015; Avci and Kelleci, 2016). Instead, employment status seems to play a crucial role in alexithymia, probably as employed patients may have more problems to both manage and integrate their own disease in everyday life. However, this data is derived from only one study (Avci and Kelleci, 2016) and it needs further scientific investigation.

Some interesting, but not exhaustive, findings refer to the association of alexithymia and lifestyle factors, such as reduced physical activity (Fares et al., 2019; Lai et al., 2019). Since alexithymia may involve a reduced capacity to deal with emotional burden, patients may perceive the stressful rigors of diabetes management to a greater extent without complying with the required lifestyle changes (Dipnall et al., 2015).

Focusing T2DM, disease duration appeared in some but not all studies associated with alexithymia, and T2DM treatment (diet, oral anti-diabetics, and subcutaneous insulin) did not show a significant role based on the empirical observations (Luca et al., 2015; Avci and Kelleci, 2016).

Interestingly, more robust evidence emerges with regard to the association between alexithymia and glycemic control, with generally large-sized effects (Luca et al., 2015; Avci and Kelleci, 2016; Fares et al., 2019). Based on the examined research findings, alexithymic traits represent a potential predictor of poor glycemic control; as well, good glycemic control is found to be protective against the presence of alexithymia. Several explanations may be hypothesized. On one hand poor awareness of bodily sensations in alexithymic patients may negatively impact coping strategies in T2DM management relatively to both disease knowledge and capabilities of self-care (Topsever et al., 2006). Besides, since alexithymia involves scarce emotional competence patients with alexithymic traits may be less prone to recognize their illness and adequately follow the medical regimen, overall showing worse glycemic control (Caputo, 2013; Marchini et al., 2018). On the other hand, poor glycemic control in diabetes could in turn negatively affect body functions, particularly cognitive and emotional processing, because of vascular and neuronal mechanisms, thus resulting in greater alexithymia levels (Contreras and Gutiérrez-García, 2017; Fares et al., 2019). The negative relationship between alexithymia and glycemic control may be supported also in the light of the association between alexithymia and increased hospitalization due to acute and chronic diabetes complications, as suggested by some studies (Fares et al., 2019; Lai et al., 2019).

The current review provides solid empirical evidence across the examined studies also regarding the relationship between alexithymia and psychological distress. In detail, alexithymia is found to strongly correlate with depression levels to a clinically significant extent, generally with moderate or large effect sizes. This could depend on the inherent difficulties dealing with painful emotions of grief and loss, thus preventing the individuals from psychological mourning elaboration, whose depression is a signal both in T2DM and other chronic conditions (Coughlin, 2011; Marchini et al., 2018; Caputo, 2019; Vicario et al., 2019; Martino et al., 2020a). We also confirm evidence of a high correlation between alexithymia and anxiety, especially with the difficulty identifying feelings (Martino et al., 2019a). This could suggest the impaired ability to monitor body signals may prevent from making sense of illness, potentially increasing perceived diabetes-related stress (Knowles et al., 2020). These findings highlight alexithymic patients to have poor quality of life (Luca et al., 2015) and poor mental well-being associated with their perceived health-status (Martino et al., 2019a). In particular, difficulty in identifying feelings seems to play a relevant negative role (Martino et al., 2019a), thus supporting the previously discussed hypothesis about mourning illness (Hyphantis et al., 2005, 2013; D'Alberton et al., 2012; Conti et al., 2016; Marchini et al., 2018; Velotti et al., 2019). Based on the present study findings, psychotherapeutic or psychological

interventions could be proposed aimed at fostering patients' diabetes adaptation according to a psychodynamic perspective. Such interventions could work on depressive and anxiety feelings over the course of the disease, which may prevent from accepting illness and enacting consistent self-care behaviors, with negative consequences on treatment adherence and diabetes management (D'Alberton et al., 2012; Marchini et al., 2018). Especially, therapeutic writing and expressive disclosure interventions could facilitate the emotional processing of thoughts and feelings about diabetes, enabling the capacity for introspection and thus ensuring biographical continuity and coherence to the self over the course of the chronic condition (Caputo, 2019). In such a way, it could be possible to contrast potential processes of personification and protagonization of illness in narrative, thus contributing to repair a defective identity that is disrupted by the disease (D'Alberton et al., 2012; Marchini et al., 2018).

This systematic review has some limitations that should be noted. The low number of retrieved articles, even due to the selection of available literature from 2015 to date, which on the other side allowed to highlight results from very recent publications, even in line with the most recent progress in the clinical management of T2DM. There is a strong heterogeneity of the examined studies regarding the adoption of inclusion/exclusion criteria, the size and characteristics of the samples, the diverse data analyses conducted, and the different assessment tools used to inspect other lifestyle and psychological variables. As well, it should be acknowledged that the cross-sectional (rather than longitudinal) design of the examined studies does not allow generalization and inference on the causal relationship between T2DM and alexithymia, but just allows an explorative inspection needing confirmation in further research. In addition, the lack of experimental and evaluation studies does not consent getting exhaustive conclusions about the "true" impact of alexithymia, that could be biased by its interrelations with other relevant aspects of the psychological status. Then, the self-report nature of TAS-20 represents a further limitation because a multi-method approach is recommended in assessing alexithymia since it has been argued that individuals with alexithymic characteristics could not give an accurate estimation of their affective disturbances due to their reduced emotional insight (Lumley et al., 2005).

CONCLUSION

In conclusion, this systematic review provides an overview and offer new insights about the clinical need of assessing alexithymia in patients suffering T2DM as its prevalence and strong association with ineffective disease management and psychological distress. Currently, there is empirical evidence which indicates the association between poor glycemic control and psychological distress (e.g., depression, anxiety, quality of life) in patients with T2DM with high alexithymia levels. However, the significance of several aspects remain unclear. Specifically, further studies are needed to improve evidence concerning the role of age, gender, additional diabetes- or treatment-related information, and lifestyle factors, as to provide new research directions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

GM made significant contribution to the conception and design of the systematic review, acquisition, qualitative analysis, and synthesis of data by drafting both the first and revised versions of the manuscript. ACap contributed to the acquisition, qualitative analysis, and synthesis of data by drafting the first version of the manuscript. CV and ACat gave significant contribution to draft part of the manuscript. PS and MQ revised manuscript for intellectual content 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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Mindfulness, Age and Gender as Protective Factors Against Psychological Distress During COVID-19 Pandemic

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Objective: Mindfulness disposition is associated with various psychological factors and prevents emotional distress in chronic diseases. In the present study, we analyzed the key role of mindfulness dispositions in protecting the individual against psychological distress consequent to COVID-19 social distancing and quarantining.

Methods: An online survey was launched on March 13, 2020, with 6,412 responses by April 6, 2020. Socio-demographic information, exposure to the pandemic, and quarantining were assessed together with psychological distress and mindfulness disposition. Multivariate linear regression analysis was performed to study the influence of predictive factors on psychological distress and quality of life in Italian responders during the early days of lockdown. Pearson correlations were calculated to study the relationship between mindfulness and psychiatric symptoms.

Results: Multivariate linear regression run on socio-demographics, COVID-19-related variables, and mindfulness disposition as moderators of overall psychological distress showed that mindfulness was the best predictor of psychological distress ($\beta = -0.504$; $p < 0.0001$). High negative correlations were found between mindfulness disposition and the overall Global Severity Index ($r = -0.637$; $p < 0.0001$), while moderate to high associations were found between mindfulness and all SCL-90 sub-scales.

Discussion: Findings showed that high dispositional mindfulness enhances well-being and helps in dealing with stressful situations such as the COVID-19 pandemic. Mindfulness-based mental training could represent an effective intervention to stem post-traumatic psychopathological beginnings and prevent the onset of chronic mental disorders.

Keywords: mindfulness, COVID-19, pandemic, meditation, psychological distress, SCL-90, MAAS, adjustment

INTRODUCTION

The current global COVID-19 pandemic has negatively impacted mental health worldwide. In order to respond most effectively to this emergency, an immediate international response from mental health professionals is needed (Aafjes-van Doorn et al., 2020; Conversano et al., 2020b; Fisher et al., 2020; Holmes et al., 2020; Muratori and Ciacchini, 2020). Researchers across the world are promptly trying to address this issue by screening the psychological impact of social distancing and quarantining (Brooks et al., 2020; Orrù et al., 2020; Poli et al., 2020). Results from early studies using social media like Twitter and Weibo data have found that posts related to negative emotions and sensitivity to social risks have greatly increased during lockdown (Kwon et al., 2020; Li et al., 2020). Consistent with these findings, another study on the psychological impact of COVID-19 among Italians during the first week of lockdown has found that 40% of participants reported high psychological distress and about 30% showed clinically significant post-traumatic symptoms (Marazziti et al., 2020). Conversely, adaptive defensive functioning has been found associated with better adjustment and fewer post-traumatic symptoms (Di Giuseppe et al., 2020a). In the present study, we have analyzed the impact of mindfulness dispositions as a protective factor against psychological distress.

In reference to the so-called protective factors in a lowered stress impact perspective, the literature identifies some human abilities already described in ancient times (i.e., Buddhism and other contemplative traditions), which may represent some valid tools in dealing with stress. These abilities may vary from different cognitive processes such as attention, memory, and thought. One of these cognitive processes may be represented by *mindfulness*, the experience of awareness which is activated by purposely paying attention to what occurs in the present, with a non-judgmental attitude (Kabat-Zinn, 2015). In other words, mindfulness may be defined as a process involving attention, awareness, and an open-minded acceptance of the present moment; it concerns the quality of consciousness itself and it is not identified with reflective thought but "offers a bare display of what is taking place" in the moment of observation (Shear and Jevning, 1999, p. 204).

Many researchers, in the last 30 years, have studied this human ability, identifying its intrinsic nature in the human being and its possible enhancement through environmental and behavioral training (Brown and Ryan, 2003; Kabat-Zinn, 2003). To date, this mindfulness ability seems to be related to other psychological constructs such as emotional intelligence, vivid perception, receptive attention, personality traits, and defense mechanisms (Salovey et al., 1995; Costa and McCrae, 2008; Marazziti et al., 2015; Di Giuseppe et al., 2019a). Mindfulness has also been proven to represent a good predictor of depression, anxiety, stress, and well-being in association with self-compassion, self-efficacy, and gender (Soysa and Wilcomb, 2015; Conversano et al., 2020a). Dispositional mindfulness has the potential to be used as treatment for stress-related and other mental health disorders (Baer, 2003; Chang et al., 2004) and is effective in the enhancement of immune function (Davidson et al., 2003) and self-regulation, through the training of attention control, emotion regulation, and self-awareness (Tang et al., 2015; Geng et al., 2019). Interestingly, similar findings were shown in recent studies concerning the key role of defense mechanisms and related psychological functions in chronic illness (Di Giuseppe et al., 2018, 2019b, 2020b; Catalano et al., 2019; Conversano, 2019; Merlo, 2019; Marchi et al., 2019; Lenzo et al., 2020; Martino et al., 2019a,b, 2020a). In particular, mood disorders seem to negatively affect physical and psychological response to treatment in chronic patients (Marazziti et al., 2008; Mula et al., 2008; Dell'Osso et al., 2012; Piccinni et al., 2012; Veltri et al., 2012; Martino et al., 2019c, 2020b). Recent studies demonstrated that mindfulness disposition is related to anxiety and depression and this is observable among different clinical populations (Idusohan-Moizer et al., 2015; Zhang et al., 2015; Lam et al., 2020). Several systematic reviews and meta-analyses showed significant beneficial effects on depressive and anxiety symptoms in patients treated with mindfulness-based interventions (Strauss et al., 2014; Chu et al., 2018).

As regards the measurement of mindfulness levels, there are different validated tools available for scientific research, each of which focuses on different operational definitions (Baer et al., 2004; Baer et al., 2006). The Mindful Attention Awareness Scale (MAAS; Brown and Ryan, 2003) is a psychological instrument to assess the presence or absence of attention to and awareness of what is occurring in the present moment for the participants. It focuses on the above-mentioned core characteristic of mindfulness, which has a dispositional quality. From the validation study of the MAAS, this unique quality of consciousness seems to be related to, and predictive of, a variety of self-regulation and well-being constructs such as optimism, satisfaction, vitality, and self-esteem, and negatively correlated with anxiety, depression, impulsiveness, and self -monitoring (Ryan and Deci, 2000; Brown and Ryan, 2003).

In the present study, regarding the Italian population during the COVID-19 pandemic, we sought to (1) identify individuals at higher risk for psychological distress while measuring the weight of mindfulness disposition in protecting their mental health and (2) assess the relationship between mindfulness and several psychiatric symptoms of distress. Regarding the first hypothesis, we expected that socio-demographic characteristics and lockdown duration would negatively affect psychological well-being, while higher mindfulness would lower the levels of distress. Regarding the second hypothesis, we expected that higher mindfulness disposition would be associated with lower self-rated psychiatric symptoms and lower overall psychological distress.

MATERIALS AND METHODS

Participants

From March 13 to April 6, 2020, we collected 6,412 responses from people living in Italy to an online survey about the psychological impact of COVID-19 during the lockdown. Responders were mostly middle-aged adults between 30 and 50 years old, while approximately 33 and 27% were younger and older, respectively. Most of the sample was represented by

TABLE 1 | Descriptive statistics of responders' socio-demographic characteristics (*N* = 6,412).

		N	%
Age			
	<30	2,099	32.7
	30–50	2,572	40.1
	>50	1,741	27.2
Gender			
	Male	1,604	25.0
	Female	4,808	75.0
Location			
	North Italy	1,603	25%
	Central Italy	3,463	54%
	South Italy	1,346	21%
Living with			
	Close relatives	4,508	70.3
	Partners	838	13.1
	Roommate	286	4.4
	Alone	780	12.2
Having children			
	Yes	2,619	40.8
	No	3,793	59.2
Positive cases among relatives and friends			
	Yes	417	7%
	No	5,995	93%
Deaths among relatives and friends			
	Yes	167	3%
	No	6,245	97%

females, living with close relatives, without children (see **Table 1** for descriptive statistics). Participants prevalently came from Central Italy (*N* = 3,463; 54%), whereas 25% (*N* = 1,603) and 21% (*N* = 1,346) were in the North and the South of Italy, respectively. The rates of reported positive cases and deaths among close relatives or friends were about 7% (*N* = 417) and 3% (*N* = 167), respectively.

Measures

To evaluate psychological distress and individual adaptive responses we conducted a survey exploring socio-demographic information, COVID-19-related information (i.e., presence/absence of positive cases or death among relatives or friends), psychological distress, and mindfulness disposition. The Italian version of the Symptoms Checklist-90 (SCL-90; Derogatis et al., 1973; Cassano et al., 1999) and the Mindfulness Attention Awareness Scale (MAAS; Brown and Ryan, 2003; Veneziani and Voci, 2015) were used for the assessment of psychological variables.

The *Symptoms Checklist-90* is a 90-item 5-point scale assessing psychopathological and somatic symptoms occurring during the past week. Even if it does not control for deceptive responses (Sartori et al., 2017), in this specific setting is adequate given the absence of faking proneness in respondents. The SCL-90 provides a Global Severity Index (GSI) and nine subscale scores for psychiatric symptoms, such as Somatization (SOM), Obsessive Compulsive Disorder (O-C), Interpersonal Sensitivity (I-S), Depression (DEP), Anxiety (ANX), Hostility (HOS), Phobic Anxiety (PHOB), Paranoid Ideation (PAR), and Psychoticism (PSY). Validity and reliability of the scale have been largely documented (Derogatis et al., 1976; Derogatis and Cleary, 1977; Bonicatto et al., 1997; Lara et al., 2005).

The *Mindfulness Attention Awareness Scale* is a 15-item single-dimension measure of the frequency of open and receptive attention to, and awareness of, ongoing events and experience using a 6-point Likert. All items are presented as negative descriptions of mindfulness, so higher scores indicate less mindfulness. For the purpose of the study, we adapted the MAAS, resulting in a reversed 5-point Likert scale, so higher scores indicated greater mindfulness. The MAAS is a reliable instrument with a Cronbach's α of 0.87. Adequate test-retest reliability, and convergent as well as discriminate validity have been reported (Black et al., 2012).

Procedure

An online questionnaire was launched online on March 13, 2020, at 17:00 (GMT + 1), 2 days after the Italian Government Decree of lockdown for slowing the diffusion of the COVID-19 outbreak. Participants were recruited using snowball sampling among all Italian residents living in Italy at the time of data collection. They were informed about the purpose of the study and asked to give their approval on personal data treatment. All procedures followed the ethical standards and were approved by the Ethics Committee of the University of Pisa (n. 0036344/2020).

Statistical Analyses

Descriptive data are presented as means, standard deviations, 95% confidence intervals, absolute and relative frequencies. The Anderson-Darling test and Normal P-P plot were used to verify normality of distributions. Pearson correlation coefficients were calculated, *t*-test and simple linear regressions were performed to study the relations between the variables and the outcome. Multivariate analysis was carried out to study the influence of predictive factors on psychological distress. Tolerance index and Variance Inflation Factor (VIF) were calculated to verify the level of correlation between predictors. Tolerance values were > 0.5 and VIF values were < 2, these results showed no evidence of multicollinearity. Goodness of fit of the multivariate analysis was verified, adjusted R^2 resulted 0.43, showing a good level of fit model. *Post hoc* power analysis was used to evaluate the sample size and the probability of type II error; the range of statistical power was 0–1 and the power of the sample was 1. The significance level was set to 0.05 and the analyses were performed with R version 4.0.0.

RESULTS

Table 1 shows descriptive statistics for socio-demographic characteristics of participants. In line with previous studies, young, female, living with parents, and not having children were more frequent among responders. Descriptive statistics for psychological variables are displayed in **Table 2**.

TABLE 2 | Descriptive statistics of responders' psychological characteristics (*N* = 6,412).

	Mean	*SD*	95% interval confidence	
			Lower	Upper
Mindfulness (MAAS)	2.881	0.653	2.865	2.897
Psychological distress (SCL-90 GSI)	0.730	0.536	0.717	0.743
SCL-90 SOM	0.622	0.605	0.607	0.637
SCL-90 O-C	0.872	0.683	0.855	0.889
SCL-90 INT	0.607	0.588	0.592	0.621
SCL-90 DEP	0.977	0.746	0.958	0.995
SCL-90 ANX	0.860	0.694	0.843	0.877
SCL-90 HOS	0.650	0.613	0.635	0.665
SCL-90 PHOB	0.478	0.548	0.465	0.492
SCL-90 PAR	0.713	0.665	0.697	0.730
SCL-90 PSY	0.509	0.522	0.497	0.522
SCL-90 SLEEP	1.076	0.982	1.052	1.100

TABLE 3 | Univariate linear regressions for socio-demographic variables and mindfulness predicting psychological distress.

	Global Severity Index (GSI)					
	β	*SE*	*t*	*P*	95% CI	
Age	−0.072	0.004	−16.120	<0.0001	−0.081	−0.063
Gender (female)	0.175	0.015	11.436	<0.0001	0.145	0.205
Having children	−0.141	0.013	−10.446	<0.0001	−0.167	−0.114
Location Central Italy	−0.017	0.018	−0.996	0.319	−0.052	0.017
Location South Italy	−0.039	0.021	−1.863	0.063	−0.079	0.002
Positive cases	0.046	0.027	1.682	0.093	−0.008	0.099
Deaths	0.040	0.042	0.939	0.348	−0.043	0.122
Living with lover	0.133	0.033	4.079	<0.0001	0.069	0.197
Weeks in lockdown	0.052	0.008	6.183	<0.0001	0.036	0.069
Mindfulness (MAAS)	−0.504	0.008	−64.169	<0.0001	−0.519	−0.488

Location Central Italy and Location South Italy resulted non-significant in comparison with Location North Italy.

TABLE 4 | Multivariate linear regression for socio-demographic variables and mindfulness predicting psychological distress.

	Global Severity Index (GSI)					
	β	*SE*	*t*	*P*	95% CI	
Age	−0.039	0.005	−8.320	<0.0001	−0.048	−0.030
Gender (female)	0.078	0.012	6.570	<0.0001	0.054	0.101
Living with lover	−0.040	0.016	−2.527	0.012	−0.072	−0.009
Weeks in lockdown	0.050	0.006	7.846	<0.0001	0.038	0.063
Mindfulness (MAAS)	−0.504	0.008	−64.169	<0.0001	−0.519	−0.488
Having children	−0.021	0.014	−1.478	0.140	−0.050	0.007

Living with lover is significant in comparison to living with parents, whereas either living alone or with roommates resulted non-significant in comparison to living with parents.

TABLE 5 | Pearson correlations between mindfulness disposition (MAAS) and psychological distress (SCL-90).

	MAAS (*N* = 6,412)	
	r	*p*
GSI	−0.637	<0.0001
SCL-90 SOM	−0.466	<0.0001
SCL-90 O-C	−0.627	<0.0001
SCL-90 INT	−0.551	<0.0001
SCL-90 DEP	−0.565	<0.0001
SCL-90 ANX	−0.536	<0.0001
SCL-90 HOS	−0.487	<0.0001
SCL-90 PHOB	−0.415	<0.0001
SCL-90 PAR	−0.533	<0.0001
SCL-90 PSY	−0.593	<0.0001
SCL-90 SLEEP	−0.386	<0.0001

Mindfulness mean scores assessed around normative values for healthy individuals (M = 2.881; SD = 0.653), while psychological distress mean score ranged slightly below the cut-off for clinical significance (M = 0.730; SD = 0.536). These results indicated that responders represented a community sample experiencing a stressful life event such as the lockdown as a consequence of the COVID-19 outbreak.

Tables 3, **4** show results from univariate and multivariate linear regression run on socio-demographic variables and mindfulness disposition as predictors of overall psychological distress are displayed. **Table 3** shows results of preliminary univariate linear regression analyses of all socio-demographic variables on the GSI. We entered in the multivariate linear regression model only variables that resulted significantly related to the GSI. Variables included were age, gender, quarantine, people living with, having children, and mindfulness. **Table 4** shows that all factors resulted significantly, with the only exception of having children that was no longer significant in the final model. Mindfulness resulted the best predictor of GSI, about 10 times more effective than other predictors included. Each increase of one unit of MAAS results in a decrease of -0.5 in GSI (β = -0.504; $p < 0.0001$). Conversely, quarantining negatively affected mental health, increasing GSI of 0.05 for each week passed in lockdown. Younger subjects and females were at higher risk for mental health problems, while living with one's spouse resulted in them feeling slightly protected in terms of psychological well-being. VIF < 2 demonstrated low collinearity level between independent variables.

Table 5 shows Pearson correlations between MAAS and SCL-90. High negative correlations were found for mindfulness disposition and overall psychological distress (r = -0.637; $p < 0.0001$), obsessive compulsive (O-C; r = -0.627; $p < 0.0001$), and psychoticism (PSY; r = -0.593; $p < 0.0001$). The remaining SCL-90 sub-scales showed moderate negative correlations ranging from 0.386 to 0.565 (all $p < 0.0001$). In descending order of magnitude they were: depression (DEP), interpersonal sensibility (INT), anxiety (ANX), paranoid (PAR), hostility (HOS), somatization (SOM), phobic anxiety (PHOB), and sleep disturbance (SLEEP), with a very tight 95% confidence interval demonstrating excellent goodness of fit.

DISCUSSION

The current study contributes to a growing literature on the benefits of protective factors on psychological functioning during high stress situations. According to our findings, dispositional mindfulness may represent a stable protective factor from the current intensity of mental distress of individuals; in fact, increasing levels of mindfulness corresponded to significantly decreased mental discomfort.

With regard to our first hypothesis which stated that certain individuals are at higher risk for psychological distress, whereas others show better adjustment to stressful situations, the results indicated that dispositional mindfulness, older age, living with loved one, and being a parent were protective factors, while female gender and lockdown duration increased the risk of psychological distress. Each increase of one unit of MAAS results in a decrease of -0.5 in GSI ($\beta = -0.504$; $p < 0.0001$), indicating that mindfulness disposition is extremely important as a psychological resource that helps the individual to manage stressful situations (Bränström et al., 2011; Rasmussen and Pidgeon, 2011; Bao et al., 2015; Dixon and Overall, 2016). Conversely, quarantining negatively affected mental health, increasing GSI of 0.05 for each week passed in lockdown. Consistent with previous studies (Di Giuseppe et al., 2019c, 2020c; Carmassi et al., 2014, 2018), younger subjects and females were at higher risk for mental health problems, while living with one's spouse resulted in them feeling slightly protected in terms of psychological well-being. The protective factor of mindfulness disposition and training has already been shown in previous literature, influencing positively memory function, cognitive resilience, mental health, emotional balance, and high stress functioning, also decreasing anxiety, depression, and burnout levels (Jha et al., 2010, 2017; Abenavoli et al., 2013; De Frias and Whyne, 2015; Westphal et al., 2015; Xu et al., 2017). This particular result is extremely significant as it shows that "being mindful" helps in dealing with stressful situations such as the one we are experiencing at the moment and leaves open the possibility for mental health professionals to use mindfulness-based mental training to stem the post-traumatic psychopathological beginnings that are likely to manifest in the future.

In addition to mindfulness, other protective factors emerged from our investigation. Findings showed that with increasing age, individuals showed less psychological distress. As other studies have already demonstrated, age of onset is exceedingly early for some psychopathological disorders such as anxiety, substance use, impulse control, and mood disorders (Kessler et al., 2007; Jones, 2013). Nevertheless, it has been proven that after an emergency due to natural disasters, older adults have increased resiliency to psychopathologies such as post-traumatic stress disorder, mood, and anxiety disorders (Acierno et al., 2006). Taken together, our results confirm a greater resilience in adults compared to young people with regard to high stress functioning, providing an important reflection on the direction of the efforts that mental health professionals will have to address their attention to soon. Furthermore, the social condition (cohabitants' situation during quarantine) could represent a protective factor against psychological distress. Not surprisingly, amongst the four conditions proposed in our survey, "living with a partner" predicted lower distress during the COVID-19 quarantine. According to previous studies, social relations are indeed a protective factor for mental health, increasing resilience (Fuller-Iglesias et al., 2008) but our findings showed that to be significant, it should come from loved ones. In fact, separation from loved ones seems to be the crucial psychological distress factor during quarantine, despite the support of new devices that are keeping us connected (Maunder et al., 2003; Manuell and Cukor, 2011; Brooks et al., 2020). Furthermore, 'being a parent' seems to be a protective condition against mental illness, as already reported in other studies (Helbig et al., 2006; Nelson et al., 2014).

Conversely, gender and lockdown duration were good predictors of higher distress among Italians. Female gender seems to be solidly related with higher psychological distress than male gender. As well known, men and women experience different kinds of mental health problems; females tend to exceed males in internalizing disorders with higher prevalence of depression and anxiety (Rosenfield, 1999; Rosenfield and Mouzon, 2013). This gap narrows with the temporal and spatial variation in gender role traditionality (Seedat et al., 2009). There is no doubt that particular attention should be paid to women in this crucial period, who, in addition to being at greater risk of developing a mood disorder or suffering from psychological distress, are unfortunately the main victims of domestic violence (Bradbury-Jones and Isham, 2020; Taub, 2020). Furthermore, the economic downturn caused by this emergency is more likely to impact sectors with high female employment shares, together with the increasing needs in childcare (Alon et al., 2020). Finally, our findings suggested that lockdown duration has a negative impact on mental health; a previous study displayed in the first phase of the Italian quarantine had already reported that individuals in quarantine experienced negative psychosocial changes such as sleep disturbances, post-traumatic symptoms, depression, and anxiety which all have a massive impact on well-being (Brooks et al., 2020; Cellini et al., 2020; Wang et al., 2020; Di Giuseppe et al., 2020d).

Our second hypothesis of a strong negative relationship between mindfulness and psychiatric symptoms of distress was fully confirmed. Mindfulness was found to be negatively correlated with all the analyzed subscales. In particular, individuals with lower mindfulness disposition are more likely to present thoughts, impulses, and actions that are experienced as irresistible but are of an unwanted nature, and cognitive attenuation (Obsessive-compulsive subscale). In addition, lower mindfulness predicted the experience of withdrawal, isolation, and a schizoid lifestyle and also on first-rank schizophrenia symptoms such as hallucinations and thought-broadcasting (Psychoticism subscale; Matti, 2003). Moreover, significant moderate correlations were found for all psychiatric symptoms assessed with the SCL-90, with greater magnitude on interpersonal sensitivity, depression, and anxiety. Results demonstrated that a higher disposition toward mindfulness may represent a protective factor against anxiety, dysphoric mood, lack of motivation, loss of vital energy, feelings of hopelessness, and cognitive and other somatic correlates of

depression, as already shown in previous studies (Teasdale et al., 2000; Evans et al., 2008; Walsh et al., 2009; Deng et al., 2014; Segal and Teasdale, 2018).

The present study has several strengths and innovative features, as well as a number of limitations. First, the cross-sectional research design does not allow us to determine causal relationships between studied variables (Pearl, 2010; Orrù et al., 2020,a,b). Moreover, we used a non-randomized sampling method, the so-called snowball sampling, which could be possibly biased by uncontrolled variables. Furthermore, all measures are self-reported and thus they might be biased by the responders' self-observation attitude. Finally, psychological information was collected online and without any independent evaluation of the health status of the respondents.

Despite all the above, this study indicates that mindfulness and socio-demographic characteristics play a key role in moderating the experience of COVID-19-related distress. Mindfulness dispositions and practice, as with other psychological resources (Lingiardi et al., 2010; Fonagy and Bateman, 2016; Prout et al., 2019; Di Giuseppe et al., 2020e), enhances adaptation and leads to a better adjustment to stress (Maffei et al., 1995; Di Giuseppe et al., 2019a; Marazziti et al., 2020). In order to stem the psychopathological consequences lying ahead in the future due to the traumatic nature of the recent pandemic and quarantine, we therefore suggest paying accurate attention to mindfulness disposition and training, with the purpose of enhancing resilience to high-stress events and preventing the onset of chronic mental disorders.

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 studies involving human participants were reviewed and approved by the Ethics Committee of the University of Pisa. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CC and MD conceived the assessment. MM contributed to the data analysis. RC contributed to the data interpretation. CC, MD, MM, RC, AG, and GO drafted the manuscript. All authors critically revised the manuscript and approved the final version to be published.

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Type C Personality: Conceptual Refinement and Preliminary Operationalization

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In this paper, we have presented our proposal for reconceptualization and operationalization of Type C (cancer-prone) personality. Based on theoretical analyses, taking into account both the literature on Type C and models of personality structure, we have proposed a two-facet structure of Type C, comprising *Submissiveness* (the interpersonal aspect) and *Restricted Affectivity* (the intrapersonal aspect). The study devoted to the validation of the measure of Type C involved 232 participants aged 18–70 (*M* = 29.35, *SD* = 8.93; 54% male). We used (a) our proposed measure of Type C personality and (b) the Circumplex of Personality Metatraits Questionnaire (CPM-Q-SF; Strus and Cieciuch, 2017), assessing personality metatraits. The measure of Type C proved to have acceptable internal consistency (Cronbach's alpha was 0.85 for Submissiveness and 0.78 for Restricted Affectivity). The measurement model in confirmatory factor analysis with two latent variables proved to be well-fitted to the data. We have also confirmed the hypothesis concerning the location of the two facets of Type C personality close to each other in the theoretically predicted area between the Delta-Plus/Self-Restraint and Beta-Minus/Passiveness metatraits (in the Circumplex of Personality Metatraits). The clinical value of the theoretically refined Type C can be tested in the next step in research on patients with cancer.

Keywords: Type C personality, Circumplex of Personality Metatraits, submissiveness, restricted affectivity, cancer-prone personality

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INTRODUCTION

Type C: The Search for Psychological Determinants of Cancer

The belief that somatic diseases depend also on psychological factors has been the underlying assumption of many studies that sought to identify those personality characteristics that increased the risk of specific somatic diseases or were responsible for general susceptibility to diseases (Friedman and Rosenman, 1959; Greer and Morris, 1975; Denollet et al., 1995; Dolińska-Zygmunt, 2001b; Ogińska-Bulik and Juczyński, 2008; Horwood et al., 2015; Šmigelskas et al., 2015). One of the personality constructs claimed to be associated with the occurrence of cancer is Type C personality (Eysenck, 1994; Bozo et al., 2014; Habibi et al., 2015), also referred to as Type C behavior (Greer and Watson, 1985), Pattern C behavior (Dolińska-Zygmunt, 2001b), or cancer-prone personality (Eysenck, 1994; Watson et al., 1999).

The introduction of Type C into the literature is usually attributed to Greer and Morris (1975), who conducted research on a sample of women with breast cancer and found the co-occurrence of cancer with a certain pattern of behavior associated with abnormal expression of emotions, which they later named Type C behavior (Greer and Watson, 1985). The characteristics of Type C and its relations to other personality types and traits were also the subject of the work of Eysenck (1991). What is particularly often provided in the literature is the graphic presentation of Types C (cancer-prone personality), Type A (coronary heart disease-prone personality), and Type B (normal, not disease-prone personality) in relation to the traits of extraversion and neuroticism, proposed by Eysenck (1991), as shown in **Figure 1**.

According to this perspective, cancer-prone personality (Type C) is associated with neuroticism and introversion, while coronary heart disease-prone personality is associated with neuroticism and extraversion (Eysenck, 1991). Empirical results, however, did not always confirm this pattern of theoretical relations, and sometimes, they even directly contradicted it. Already in the first study of Kissen and Eysenck (1962) conducted on a sample of men with lung cancer, it turned out that the occurrence of cancer was related to a low rather than high level of neuroticism. Also in his other publications, Eysenck (1985) discussed studies in which it was low neuroticism (e.g., Morris et al., 1981) or high extraversion that was significantly related to cancer incidence (e.g., Coppen and Metcalfe, 1963; Hagnell, 1966). There were attempts to explain the empirically found negative relationship between neuroticism and cancer as stemming from the emotional repression that may accompany low neuroticism (Eysenck, 1991) and the negative link between cancer and introversion as due to the better condition of the immune system in introverts (Eysenck, 1985).

A number of further studies on cancer patients revealed additional links between Type C and psychosocial factors but they were not always consistent either. For example, a study by Garssen and Goodkin (1999) confirmed that a low level of social support, a tendency toward helplessness, and repression of negative emotions were significant in the development of cancer. Lehto et al. (2006) found that emotional defensiveness, avoidant coping, and a high level of social support were risk factors for cancer. Reynolds et al. (2000) highlight the significance of low emotion expression and low perceived social support for the worse prognosis of patients with cancers. Furthermore, in Chinese studies on a group of patients with breast cancer (Wei et al., 2019), sense of coherence was negatively associated with Type C personality and depression, Type C personality was significantly positively associated with depression, and sense of coherence played a partial mediating role between Type C personality and depression, reducing the influence of Type C personality on depression.

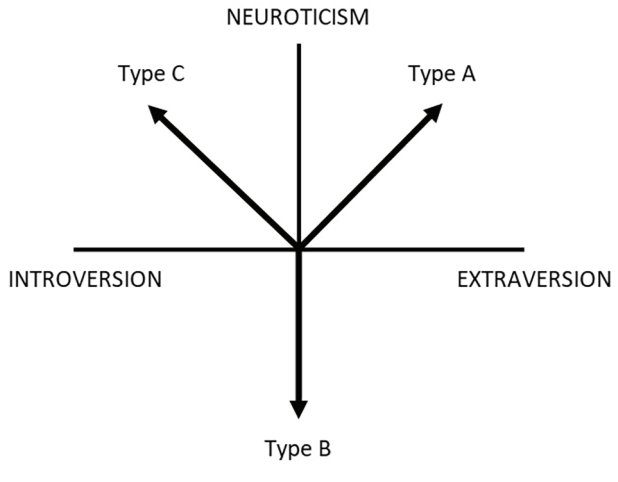

FIGURE 1 | Hypothetical relations of Types A, B, and C to extraversion and neuroticism (Eysenck, 1991).

In view of the diverse and not always consistent findings, an important research effort was the meta-analysis performed by McKenna et al. (1999), covering studies published from 1975 until 1996. It revealed that the factors significant in the development of cancer were: (a) denial/repression coping, (b) separation/loss experiences, (c) stressful life events, and (d) conflict-avoidant personality style (McKenna et al., 1999). These, however, are only four of the eight factors considered in the meta-analysis. Those that proved not to be significant were: increased anxiety/depression, childhood family environment (lack of support in childhood), difficulties with the expression of anger and resentment, and extraversion/introversion level. Another meta-analysis of 76 studies on depression and cancer mortality indicated that depression is associated with an increased risk of mortality in cancer patients and those who develop the disease (Pinquart and Duberstein, 2010). A meta-analysis conducted by Jokela et al. (2014) including six prospective cohort studies focused on the relationship between personality traits (extraversion, neuroticism, agreeableness, conscientiousness, and openness to experience) with cancer incidence and mortality as a result of cancer. The results indicated no association between any of the personality traits and the incidence of all cancers and any site-specific cancers (lung, colon, breast, prostate, skin, and leukemia/lymphoma) included in the analysis. None of the personality traits were also associated with cancer mortality.

It is worth noting that the role of personality and especially personality traits for occurrence and cancer courses are still heavily studied. In recent studies, on the one hand, de Mol et al. (2020) argue that personality traits are not associated with health-related quality of life and general quality of life, except for association between conscientiousness and physical health, in patients with advanced-stage lung cancer at the start of chemotherapy. However, on the other hand, several new studies suggest such relations; in particular, (a) neuroticism was strongly positively associated with emotional stress and mental health problems in oncological patients (Macía et al., 2020; Perry et al., 2020) and negatively associated with better health behaviors and health (Rochefort et al., 2018); (b) extraversion was positively associated with physical health, regardless of cancer diagnosis (Rochefort et al., 2018) and negatively associated with emotional stress and mental health problems in patients

with cancer (Macía et al., 2020; Perry et al., 2020); when combined with two personality traits, a low level of neuroticism and a high level of extraversion were associated with better mental health (Macía et al., 2020); and (c) conscientiousness was weakly negatively associated with emotional stress in patients with cancer (Perry et al., 2020) and positively with better health behaviors and health (Rochefort et al., 2018).

Other characteristics of Type C personality can also be found in the literature, similar to the above to some extent, but also going beyond those already mentioned. Type C was supposed to characterize passive individuals, incapable of helping themselves, strongly focused on other people, unable to express their emotions, anger-repressing, helpless (Temoshok, 1987; Dolińska-Zygmunt, 2001a; Kurrass, 2004; Lehto et al., 2006; Ogden, 2007; Bozo et al., 2014; Lysaker et al., 2014), self-sacrificing (Kurrass, 2004), unable to manage their psychological behaviors, submissive, pathologically kind and agreeable, cooperative, excessively patient (Temoshok, 1987; Habibi et al., 2015), and showing excessive control of emotional features (Lysaker et al., 2014; Habibi et al., 2015); it has been attributed to individuals who have strong defense mechanisms resulting in the inability to verbalize and recognize negative emotions, who show secondary negative responses such as the sense of helplessness and uselessness, who lack self-control in stressful situations, and who are submissive to authorities (Temoshok, 1987).

The above characteristics of Type C personality show its high diversity. The problem of the consistency of these characteristics has not, essentially, been addressed at the theoretical level yet. The theoretical aim of the present article is to fill this gap.

Problems Associated With Type C Personality

The literature devoted to Type C personality and its links with the occurrence of cancer contains many doubts and ambiguities. The major ones will be discussed below.

First, many research results that can be found in the literature do not confirm the significance of various components of Type C personality for the occurrence of cancer (cf. Schwarz and Geyer, 1984; Phillips et al., 2008; Archer et al., 2015). For example, Archer et al. (2015) did not confirm the link of chronic depressive symptoms with cancer occurrence. Phillips et al. (2008) found anxiety, depression, coping, and social support not to be significantly related to patients' prognosis. In the study by Schwarz and Geyer (1984), demographic characteristics, serious stressful life events, and activity control were not significantly related to the occurrence of cancer.

Second, the description of Type C personality includes various contents with unclear structure, which may stem from the method used to construct the psychological variable referred to as Type C. This method consisted in Type C personality being distinguished based on the observation of the behaviors of patients suffering from cancer (Greer and Morris, 1975; Greer and Watson, 1985). Consequently, these behaviors constituted atheoretical indicators, observed in the behavior of patients diagnosed with this disease. Type C personality was analyzed in terms of its relations to other elements of personality structure to a small extent only, and its description relied on knowledge in the field of personality psychology to a very small degree. In the literature, it is possible to find different, sometimes, divergent or even contradictory characteristics attributed to Type C as the personality basis for cancer. For instance, Garssen and Goodkin (1999) underscored the significance of low social support for the development of cancer, whereas Lehto et al. (2006) highlighted the significance of high social support. Also, unclear and full of contradictions is the role of neuroticism and extraversion, which has been discussed above (Kissen and Eysenck, 1962; Eysenck, 1985, 1991; Blanchard and Abell, 2019).

Third, there are visible deficiencies in the acceptable operationalization of Type C. Even though the construct is interesting and attracts the attention of many researchers, it has not been properly operationalized and no sound measure has been developed to assess it. One of the best-known attempts at developing such measure is the questionnaire by Watson and Greer (1983); in view of the fact that the key element in Type C personality is usually considered to be emotional repression, these authors prepared a measure of emotional control (the Courtauld Emotional Control Scale, CECS), in which they distinguished three scales: Anger Control, Anxiety Control, and Depression Control. This questionnaire, however, does not measure Type C personality directly and can be seen as assessing only one element included in this construct.

Given the breadth of the construct, its special character, and the divergences concerning both the components distinguished in it and the results of research, one can conclude that the current measurement of Type C personality is inadequate and that a comprehensive operationalization of this construct is needed. Still, what is needed before the construction of the measure is a theoretical conceptualization and a precise definition of Type C, taking into account both the existing literature about it and the current knowledge about personality structure. The theoretical conceptualization of Type C is, therefore, a precondition of solving the third problem (i.e., the lack of comprehensive operationalization). It should be performed in such a way as to solve the second problem (i.e., conceptualization taking into account the current knowledge about personality structure), which, consequently, may give hope for a solution for the first problem (i.e., relation to cancer-proneness) in future research.

Attempt to Solve the Problems Associated With Type C Personality: Conceptualization

We performed the postulated reconceptualization of Type C personality in four steps. In the first step, we compiled a list of all Type C contents and characteristics reported in the literature. In the second step, we combined those elements that were close to one another in terms of content, thus reducing the list of characteristics from Step 1. In the third step, we examined the structure of the groups distinguished and the possibilities of grouping the obtained elements into a smaller number of broader categories. In the fourth step, we linked the characteristics of Type C obtained in the previous steps with knowledge about personality structure. In particular, we looked at the characteristics of Type C from the point of view offered by the CPM

(Strus et al., 2014; Strus and Cieciuch, 2017), which, on the one hand, integrates many models of temperament, personality, emotion, motivation, health, and well-being (Strus and Cieciuch, 2017), and which, on the other hand, can be seen as a tool for testing and refining constructs in other domains (see Cieciuch and Topolewska, 2017; Rogoza et al., 2019b).

The Reconstruction of the Contents of Type C (Steps 1–3)

In the first step, we identified 20 content units in the definitions of Type C present in the literature. These were: self-sacrifice, passiveness, calmness, peacefulness, strong focus on other people, submissiveness to others, submissiveness to authorities, pathological kindness, pathological agreeableness, excessive patience, cooperativeness, inability to help oneself, repression of negative emotions, strong defense mechanisms, inability to verbalize and identify the emotions experienced, sense of helplessness and uselessness, suppression of anger, excessive control of emotional symptoms, lack of self-control in stressful situations, and low awareness of the emotions experienced (Greer and Watson, 1985; Temoshok, 1987; Dolińska-Zygmunt, 2001a; Kurrass, 2004; Ogden, 2007; Bozo et al., 2014; Lysaker et al., 2014; Habibi et al., 2015).

In the second step, we grouped the above characteristics by combining semantically close contents. This resulted in six groups: (1) excessively high (pathological) kindness; (2) self-sacrifice, strong focus on other people, inability to help oneself; (3) peacefulness and excessive patience, pathological agreeableness and submissiveness; (4) repression of negative emotions, strong defense mechanisms, suppression of anger, excessive control of emotional symptoms, calmness; (5) low awareness of the emotions experienced, inability to verbalize and identify the emotions experienced; and (6) sense of helplessness and uselessness, lack of self-control in stressful situations, passiveness.

In the third step, we divided the contents from Step 2 into two domains: interpersonal and intrapersonal. The above presentation of contents in Step 2 was organized with a view to Step 3, which is why interpersonal contents are in Groups 1–3 and interpersonal contents are in Groups 4–6. The distinction between these two domains in Type C personality was inspired by the popular model of Type D personality structure (also referred to as distress personality) proposed by Denollet (2005).

The fourth step consisted in introducing an external frame of reference into the analysis of contents attributed to Type C from the perspective of personality psychology. The description of Type C had been developed as a description of behaviors or characteristics of individuals suffering from or prone to cancer. This process of construct development should be confronted with the current knowledge about personality structure. In personality psychology, there are many different models, which – as has been proposed for some time in the literature – can be integrated in the two-factor model of personality (DeYoung, 2015; Cieciuch and Strus, 2017), whose extension is the CPM (Strus et al., 2014; Strus and Cieciuch, 2017). This model offers a theoretical matrix that enables the synthesis and organization of various kinds of constructs, frequently also making it possible to conceptualize them more precisely. What can serve as an example is the integration of different perspectives on narcissism in CPM performed by Rogoza et al. (2019b), the integration of personality disorder categories performed by Zawadzki (2016, 2017), or the synthesis of various models in the area of identity formation performed by Cieciuch and Topolewska (2017), who applied the method itself rather than the CPM itself. Below, we will present the basic assumptions of CPM and then proceed to use the model to refine the theoretical definition of Type C and to further clarify its content aspects.

The Location of Type C Personality in the Circumplex of Personality Metatraits (Step 4)

The CPM model is an extension of the two-factor model of personality (Digman, 1997; DeYoung et al., 2002; Cieciuch and Strus, 2017), depicting the structure of personality at the level of two higher-order factors (metatraits): Alpha (Stability) and Beta (Plasticity). Dimensions of Alpha and Beta constitute a system of orthogonal coordinates, in which Strus et al. (2014) additionally distinguished the dimensions of Gamma (being a reinterpretation of the general factor of personality; Musek, 2007) and Delta (being a discovery that the logic of this model led to). In each metatrait, we distinguished two poles, whose psychological contents are not reducible to a pair of opposites. This resulted in an octantal structure. The current version of the model, modified after a series of studies (Strus and Cieciuch, 2017, 2019; Rogoza et al., 2019a), is presented in **Figure 2**.

CPM emerged from the tradition of research on the five-factor model of personality (McCrae and Costa, 2003), which is why **Figure 2** presents the constellation of the Big Five traits for each metatrait. In turn, thanks to its circumplex structure, CPM creates a space in which the meaning of other constructs can be specified (see Rogoza et al., 2019a). If CPM is treated as an external system of coordinates synthesizing various models

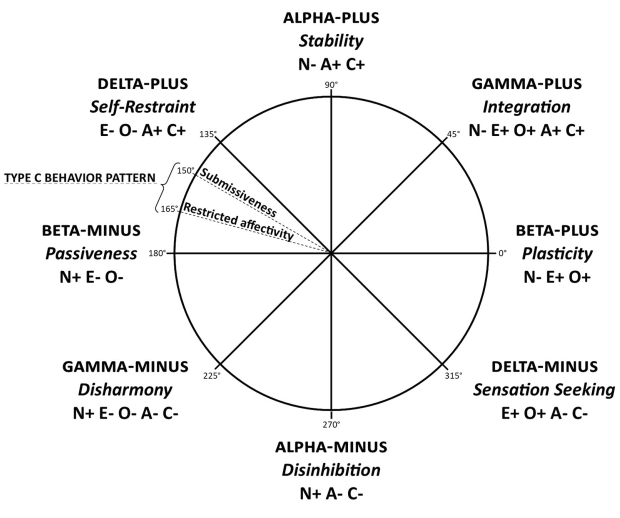

FIGURE 2 | Graphic presentation of the CPM (modified by Strus et al., 2014). N, neuroticism; E, extraversion; O, openness to experience; A, agreeableness; C, conscientiousness; +, means the positive pole of the trait; –, means the negative pole of the trait.

developed in the field of personality psychology, the question arises about the location of Type C within the circumplex. The scope of its contents presented above locates Type C between two metatraits: Delta-Plus/Self-Restraint (peacefulness, excessive patience, submissiveness, and adjustment in relations with people) and Beta-Minus/Passiveness (passiveness, helplessness and hopelessness, and low self-awareness). It seems that those personality characteristics that are situated in CPM between Delta-Plus and Beta-Minus – namely, high behavioral control, tendency to adjust oneself, conventionality, conformism, and submissiveness in interpersonal relations, repressed affectivity (both positive and negative) inhibition, apathy, and passiveness – correspond particularly strongly to the characteristics attributed to Type C personality (see Strus and Cieciuch, 2017). We considered this location of Type C personality in CPM as a broader integrating model of personality in order to theoretically clarify and refine Type C itself.

Definition of Type C

Considering the existing descriptions of Type C and its location in CPM, we propose the following definition and structure of Type C: Type C personality is composed of two facets: Submissiveness, corresponding to the interpersonal domain, and Restricted Affectivity, corresponding to the intrapersonal domain. Submissiveness and Restricted Affectivity have elements in common with both personality metratraits mentioned above, but Submissiveness is slightly closer to Delta-Plus/Self-Restraint, while Restricted Affectivity is closer to Beta-Minus/Passiveness. Submissiveness manifests itself in pathological agreeableness, compliance, kindness toward others, uncritical adjustment to them, dependence, excessive patience, peacefulness, inability to refuse, and even in excessive focus on other people and sacrificing oneself for them at the cost of one's own needs. Restricted Affectivity manifests itself in the repression and suppression of negative emotions (particularly anger), low awareness of the emotions experienced, inability to identify, name, and express them, anhedonia, passiveness, and helplessness in the face of adversities.

The Problem of the Present Study: Operationalization of Type C Personality

We subjected the conceptualization of Type C proposed above to a procedure of operationalization. In the first stage, we generated a pool of items measuring the components of Type C distinguished in the above definition (27 items for the Submissiveness scale and 17 items for the Restricted Affectivity scale). The aim of the study was to select items from the pool to be included in the final version of the questionnaire and to test its psychometric properties. We formulated the following hypotheses concerning the final version of the measure: internal consistency (measured with Cronbach's alpha) is acceptable for both scales (Hypothesis 1). The measurement model in confirmatory factor analysis with two latent variables is well-fitted to the data set (Hypothesis 2). The measurement of Submissiveness and Restricted Affectivity is invariant at configural, metric, and scalar level across gender (Hypothesis 3). Both facets of Type C are located in the CPM between Delta-Plus/Self-Restraint and Beta-Minus/Passiveness; the predicted location of Submissiveness is closer to Delta-Plus, while the predicted location of Restricted Affectivity is closer to Beta-Minus, as shown in **Figure 2** (Hypothesis 4).

MATERIALS AND METHODS

Measures

Type C Personality

In the course of work on operationalizing the definition of Type C formulated above, our team generated 44 items: 27 items for the Submissiveness scale and 17 items for the Restricted Affectivity scale. We used a five-point Likert scale (from 1 – *completely untrue about me*, to 5 – *completely true about me*). This was the initial pool, from which, in the presented study, we selected the items for the final version of the measure.

We used four selection criteria. The first criterion consisted in removing those items that significantly positively correlated with well-being, as we decided that indicators of the potentially pathological Type C personality should not be positively related to mental health symptoms. The second criterion consisted in removing the items that did not differentiate respondents' answers (low mean score and standard deviation). The items that remained after the selection performed according to the first two criteria were entered into the exploratory factor analysis for each of the two facets of Type C separately (which was the third criterion of selection). We removed the items with the lowest factor loadings. The fourth criterion was expert assessment of the contents of those items whose removal or retention was suggested by psychometric indicators. Decision concerning each item was based on theoretical reflection rather than made automatically.

Well-Being

To measure well-being, which was one of the item selection criteria for the measure of Type C, we used the following items: (1) "I often feel simply happy"; (2) "Little everyday things often give me joy"; (3) "If I could live my life again, I would change almost nothing"; and (4) "My natural mood can be called cheerfulness." Answers were given on a five-point Likert scale, from 1 (*completely disagree*) to 5 (*completely agree*); Cronbach's α was 0.70.

Personality Metatraits

To measure personality metatraits, we used the Circumplex of Personality Metatraits Questionnaire (CPM-Q-SF; Strus and Cieciuch, 2017). The questionnaire consists of 72 items describing a variety of human behaviors, feelings, thoughts, and attitudes. It measures the eight metatraits distinguished in CPM: Alpha-Plus/Stability, Alpha-Minus/Disinhibition, Beta-Plus/Plasticity, Beta-Minus/Passiveness, Gamma-Plus/Integration, Gamma-Minus/Disharmony, Delta-Plus/Self-Restraint, and Delta-Minus/Sensation Seeking. Answers were given on a five-point Likert scale from 1 (*completely disagree*) to 5 (*completely agree*). Cronbach's α of the scales ranged from 0.72 (Alpha-Plus/Stability) to 0.85 (Gamma-Minus/Disharmony).

Participants

The participants in the study were 232 individuals aged 18–70 (M = 29.35, SD = 8.93). Men (n = 126) constituted 54.3% of the sample. The participants completed the paper-and-pencil version of the set of measures; their anonymity was fully ensured. When collecting the data, we were aided by psychology students, who recruited participants among their friends, acquaintances, and distant relatives. The inclusion criteria was age (18 years or more) and approximate equal number of men and women.

RESULTS

We removed seven items after applying Criterion 1 of item selection (see description in the Measures section), and we eliminated two further items after applying Criterion 2. By applying Criteria 3 and 4, we selected 10 items for each scale, which are presented in **Table 1**.

Internal consistency (Cronbach's alpha) was 0.85 for Submissiveness and 0.79 for Restricted Affectivity, which can be regarded as acceptable values, confirming Hypothesis 1.

In categorical confirmatory factor analysis (after the inclusion of seven error correlations between items similar in meaning), the measurement model had the following measurement fit: chi^2 = 353.6, df = 162, RMSEA = 0.071 (0.061–0.082), CFI = 0.927, WRMR = 1.06. The correlation between the latent variables was 0.66. With the obtained fit indices, Hypothesis 2 can be considered as confirmed.

In order to test for measurement invariance (Hypothesis 3) across gender, we ran a multigroup confirmatory factor analysis. For technical reasons, in six cases, one answer was randomly changed to the neighboring value (e.g., answer 4 was changed to 5) in order to have all answers for all items in all groups, which is a requirement for categorical measurement invariance. We obtained the following model fit indices (a) at the configural level: chi^2 = 524.9, df = 324, CFI = 0.927, RMSEA = 0.073 (0.061–0.084); (b) at the metric level: chi^2 = 552.7, df = 342, CFI = 0.923; RMSEA = 0.073 (0.061–0.084); and (c) at the scalar level: chi^2 = 622.0, df = 400, CFI = 0.919, RMSEA = 0.069 (0.058–0.080). According to commonly used criteria (Cieciuch and Davidov, 2015), one can conclude that configural, metric, and scalar measurement invariance across gender is established. This means that both facets of Type C have the same meaning (metric invariance) and are measured in the same way (scalar invariance) across gender.

We tested Hypothesis 4 using the procedure of orthogonal Procrustes rotation (Schönemann, 1966), which Strus and Cieciuch (2017) had applied when testing hypotheses concerning the location of variables in CPM and which is recommended by Rogoza et al. (2019a) for analyzing circumplex models. The aim of the analyses was to compare the theoretical location of the facets of Type C (Submissiveness at 150 degree and Restricted Affectivity at 165 degree) with their actual empirical location. The theoretical angular location is converted in accordance with trigonometric functions into coordinates (*target matrix*), and the empirical location is the factor loadings of the analyzed variables in the two-factor solution (*obtained matrix*). Procrustes rotation rotates the empirically obtained results to the theoretically expected ones without changing the results. There are two types of Procrustes rotations: with or without row normalization. Both of them are presented in **Table 2**, while **Figure 3** presents the results with row normalization. In the rotation with row normalization, empirical loadings are transformed to the same unit-metric space as the target matrix (coordinates of 1 and +1). Factor loadings can be converted into angles, in accordance with trigonometric

TABLE 1 | Factor loadings in the confirmatory factor analysis of the questionnaire measuring Type C.

	Submissiveness	Restricted affectivity
I believe it is my obligation to put other people's needs above my own.	0.77	
In conflict situations, I always yield and submit to others.	0.70	
I can accept anything, even if it does not suit me.	0.66	
I cannot say "no" to others.	0.61	
Even if something does not suit me, I do not say it.	0.63	
I am ready to give up my plans for the good of others at any time.	0.61	
I always agree with the people important to me, because I know they are right.	0.61	
I am absolutely determined to respond to the needs of others, regardless of how I feel.	0.60	
Regardless of the situation, I wait for my turn.	0.59	
I do what I can to avoid conflicts with others.*	0.55	
All my life I have not expressed my strong emotions.		0.66
When something goes wrong, I simply come to terms with it.		0.60
To be honest, I never actually feel anger.		0.57
In difficult situation, I usually submit to the course of events.		0.56
I never actually reflect on what I feel.		0.57
No one can really make me upset.		0.53
When life is not going my way, I accept that this is how it has to be.		0.52
As a matter of fact, nothing can make me lose my temper.		0.47
When something bad happens to me, I do not think about it at all.		0.43
No matter how bad I feel, I do not show it.**		0.39

Proposed modification for use in future studies: I do what I can to avoid conflicts with others at all costs.

***Proposed modification for use in future studies: No matter how I feel, I do not show it.*

functions, and the angles can be compared with the theoretically expected ones. The degree of similarity for the entire matrix and for each variable separately is expressed as the congruence coefficient. It is assumed that a coefficient value >0.90 indicates high congruence and a value >0.95 indicates very high congruence (Barrett, 1986; Lorenzo-Seva and ten Berge, 2006). We also report R^2, which is a measure of explained variance in a given variable explained by other variables included in the model.

Table 2 presents target and obtained matrices for CPM and the two facets of Type C, followed by congruence coefficient, R^2, and empirically obtained angle.

As expected, the two facets of Type C were located close to each other, in the space between Delta-Plus and Beta-Minus, in places theoretically predicted, as evidenced by the very high congruence coefficients. The obtained results make it reasonable to consider Hypothesis 3 confirmed, but two issues should be pointed out. First, despite the high congruence coefficients, the two facets of Type C were located very close to each other – somewhat closer than expected. What we expected was that they would be located at 15-degree intervals between Beta-Minus and Delta-Plus, whereas the empirical results actually placed both facets halfway between Beta-Minus and Delta-Plus. Second, R^2 is relatively low, which means that the metatraits distinguished in the CPM do not explain a particularly high proportion of the variance in Type C. This result means that Type C is not reducible to personality metatraits, even though it is quite precisely located in the space defined by them.

DISCUSSION

In research aimed at finding the personality determinants of somatic diseases, Type C personality has been proposed and treated as a significant predictor of the incidence of cancer. The analysis of the available literature on Type C has revealed a number of characteristics postulated as elements of Type C, which were not always internally consistent and did not form a precisely defined whole. This might have been one of the causes behind the divergence, reported in the literature, in research results concerning the significance of Type C personality in predicting cancers. The relatively blurred meaning of this construct and the wide scope of characteristics included in it certainly did not facilitate its operationalization, which might have been an argument in favor of measuring only selected components rather than attempting to capture Type C as a whole.

We see our research as the first step toward clarify the theorizing and results on Type C personality. The key element of our approach was the literature-based attempt to organize the components of Type C, which led to its reconceptualization. It was on the theoretical plane, thus built that we proposed a comprehensive operationalization of Type C. The measure we developed was preliminarily found to have acceptable psychometric properties (internal consistency, factorial validity, and external validity).

Of course, what remains an unsolved problem is the significance of Type C for cancer (its appearance, development, and treatment prognosis). This problem should be addressed by future studies, or even by entire research programs. However, we propose a modification in the overall approach to this kind of research. The approach, so far, has been to find atheoretical personality indicators of cancer by looking for the typical characteristics of people suffering from it. As meta-analyses have shown, this approach did not lead to conclusive results (McKenna et al., 1999). Moreover, in some studies, no association between any of the personality traits and cancer and cancer mortality was found (Jokela et al., 2014). One of the causes might have been the primacy of direct observation over the strength of a good theoretical model. This primacy resulted in little reflection being undertaken on the theoretical meaning of Type C construct, on its internal consistency and structure, and on its location in broader models of personality structure. The approach we have proposed overcomes these weaknesses and uses the CPM (Strus et al., 2014) as the theoretical personality context and a point of reference. It should be stressed that CPM does not absorb other constructs in such a way as to make them redundant. On the contrary, it turned out that Type C was irreducible to

TABLE 2 | Target and obtained matrices for Circumplex of Personality Metatraits (CPM) and the two facets of Type C.

	Θ^T	Target matrix		Obtained matrix row		Obtained matrix normalized		R^2	Congr.	Θ^E
		F1	F2	F1	F2	F1	F2			
Delta-Plus	135	0.71	−0.71	0.64	−0.50	0.78	−0.62	0.65	0.99	128.61
Alpha-Plus	90	1.00	0.00	0.82	0.06	1.00	0.05	0.68	1.00	86.99
Gamma-Plus	45	0.71	0.71	0.68	0.52	0.80	0.59	0.74	0.99	53.58
Beta-Plus	0	0.00	1.00	0.14	0.82	0.19	0.98	0.69	0.98	10.83
Delta-Minus	315	−0.71	0.71	−0.46	0.63	−0.57	0.82	0.61	0.99	325.11
Alpha-Minus	270	−1.00	0.00	−0.89	−0.01	−1.00	0.00	0.79	1.00	270.09
Gamma-Minus	225	−0.71	−0.71	−0.60	−0.51	−0.77	−0.64	0.63	1.00	230.46
Beta-Minus	180	0.00	−1.00	0.15	−0.86	0.16	−0.99	0.77	0.98	170.89
Submissiveness	150	0.50	−0.87	0.23	−0.34	0.54	−0.84	0.17	1.00	147.52
Restricted affectivity	165	0.26	−0.97	0.21	−0.35	0.49	−0.87	0.17	0.97	150.76
Factor/overall congruence				0.98	0.96				0.99	

Target matrix is based on the hypothesized circumplex structure shown in **Figure 2**. θ^T, *angle theoretically predicted;* θ^E, *angle empirically obtained (angles in degrees); F1 and F2, factors;* R^2, *explained variance coefficients; Congr., congruence coefficients.*

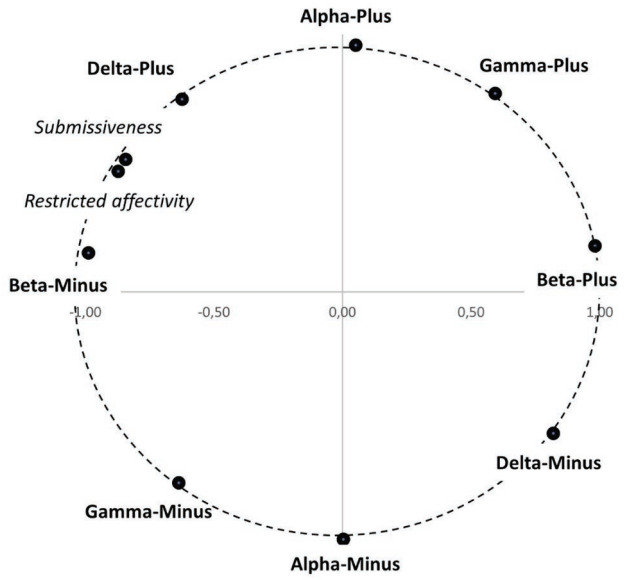

FIGURE 3 | Factor loading plots for CPM metatraits and facets of Type C from the rotated matrix with row normalization.

metatraits but it was worth applying the logic of CPM in its description and structure. This resulted in an internally consistent construct that has a well-defined structure and is clearly related to the broader model of personality.

Perhaps, it will turn out that our conceptualization and operationalization of Type C will not solve problems associated with the personality determinants of cancer but it seems that this kind of personality structure attempt is necessary. It can be said that this means giving Type C a chance as a reformed and reconceptualized theoretical construct in its role of a predictor of psychosomatic problems. Time will tell if this proves to be a chance of success or failure. It seems, however, that without this chance Type C personality would be slowly receding into the history of psychology.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Commission of Ethics and Bioethics at the Cardinal Stefan Wyszyński University in Warsaw. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

KR and AT prepared the first set of items to measure Type C. WS, KR, AT, and JC prepared the reconceptualization of Type C. KR, WS, and JC prepared the final set of items, designed the study, and run the analysis. KR in collaboration with JC and WS prepared the first version of the paper. JC revised the paper. All authors contributed to the article and approved the submitted version.

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Psychological Impact of Coronavirus Disease 2019 Among Italians During the First Week of Lockdown

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Pandemics and government-mandated quarantining measures have a substantial impact on mental health. This study investigated the psychological impact of the coronavirus disease 2019 (COVID-19) crisis on Italian residents during the first week of government-imposed lockdown and the role of defense mechanisms as protective factors against distress. In this cross-sectional study, 5,683 Italians responded to an online survey assessing socio-demographics, overall psychological distress, post-traumatic symptoms, and defense mechanisms using validated measures as the *Symptom Checklist-90* (SCL-90), the *Impact of Event Scale-Revised* (IES-R), and the *Defense Mechanisms Rating Scale-Self-Report-30* (DMRS-SR-30). Data were collected from March 13 to March 18, within the first week of lockdown in Italy. Results showed that younger age and female gender were associated with increased psychological distress. Having positive cases nearby, more days on lockdown, and having to relocate were also associated with greater distress. Higher overall defensive functioning (ODF) was associated with lower levels of depression ($r = -.44$, 95% CI –0.48, –0.40), anxiety ($r = -.38$, 95% CI –0.42, –0.35), and post-traumatic stress symptoms (PTSS) ($r = -.34$, 95% CI –0.38, –0.30). Conversely, less adaptive defensive functioning was related to greater affective distress across all domains. Each increased unit of ODF decreased the chances of developing post-traumatic stress symptoms (PTSS) by 71% (odds ratio = 0.29, $p < 0.001$, 95% CI.026,.032). The psychological impact of COVID-19 among Italians during the early weeks of government lockdown has been significant. The pandemic continues to have extraordinary mental health impact as it moves across the globe. Given the salience of defensive functioning in psychological distress, consideration of interventions that foster the use of more adaptive defenses may be an important component of building resilience amidst a pandemic.

Keywords: coronavirus disease 2019, post-traumatic stress, psychological distress, emotion regulation, defense mechanisms, quarantine, pandemic (COVID-19), lockdown

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INTRODUCTION

In March 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a pandemic. At the time of conducting this study only few countries registered positive cases and deaths for COVID-19, with Italy being the first hit European country (1). Disasters, like the one currently unfolding across the world, adversely affect well-being and overall mental health, requiring an immediate international response from multidisciplinary mental health science (2–4). The rapid spread and devastating impact of COVID-19 has resulted in social distancing, self-quarantining, and government-enforced lockdown of citizen movement. On March 9, 2020, the Italian government expanded local lockdown efforts to include all localities, requiring more than 60 million people to stay at home. The aim of this study was to assess psychological effects associated with the pandemic and their relationship to demographic and COVID-19 impact variables.

Many studies have highlighted the negative psychological impact of quarantining in concert with the obvious public health benefits (5, 6). Quarantining, coupled with other risk factors, during the severe acute respiratory syndrome (SARS) epidemic increased the odds of depressive symptoms 3 years later and a 2 to 3-fold increase in post-traumatic stress symptoms (PTSS) (7–9). Social isolation, stress, and anxiety were also associated with higher suicide rates among survivors of the SARS outbreak (10, 11). Proximity to intense outbreaks of an epidemic was also associated with higher rates of anxiety (12).

Individuals experiencing stressful life events rely on a wide range of explicit and implicit coping strategies. Active coping strategies have been shown to buffer against the impact of living amidst a global epidemic (13). Conversely, avoidant coping strategies, those that help individuals reduce emotional stress rather than dealing directly with a stressful situation, are associated with poorer psychological outcomes (13–17). Individuals who engaged in altruistic acceptance of risk during the SARS epidemic experienced lower levels of PTSS (9). The stressors associated with social isolation, quarantining, and exposure to a global health crisis do not end when the pandemic is over. Among survivors who were directly affected by the SARS epidemic, 17% had not returned to work after 1 year and had significant reductions in mental health that persisted 1 year later (18). These findings point to the importance of understanding the automatic coping mechanisms that people may employ under intense stress provoked by pandemic.

Implicit emotion regulation capacities are a central and salient aspect of how individuals manage traumatic events (19–21), particularly because they are employed automatically and often unconsciously. These cognitive and affective processes are vital components of self-regulation and mental health (22–26). There is evidence suggesting that implicit emotion regulation may be even more important to healthy mental functioning than explicit emotion regulation mechanisms (27). The inherent links between implicit emotion regulation and defense mechanisms have been explicated in detail (28). Assessing psychiatric distress and automatic mechanisms of emotion regulation, such as defense mechanisms, during the current global pandemic is of critical importance.

Objectives

Among Italians responding during the COVID-19 outbreak, this study sought to 1) examine the prevalence of symptoms of psychological distress and identify predictors of distress; and 2) evaluate different associated emotion regulation strategies (operationalized as defense mechanisms) that might impact the relationship between stress and distress. Specifically, we asked whether specific defenses might moderate the association between knowing individuals positive for COVID-19 and greater levels of symptoms of post-traumatic stress disorder (PTSD) and distress.

METHODS

Participants

Participant characteristics are presented in **Table 1**. Respondents (N = 5,683) were living in Italy, mostly young and middle-aged adults, female, living with close relatives, and without children.

TABLE 1 | Demographics and coronavirus disease 2019 (COVID-19)-related characteristics (N = 5,683).

Variable	N	%
Age		
<30	1,935	34
30–39	1,179	21
40–49	1,032	18
50–59	954	17
>=60	582	10
Gender		
Male	1,427	25
Female	4,256	75
People living at home		
Close relatives	4,023	71
Partner/lover	746	13
Roommates	254	4
Alone	660	12
Positive cases among relatives and friends		
No	5,354	94
Yes	329	6
Days on lockdown		
<=7 days	3,772	66
8–14 days	1,568	28
> 14 days	343	6
Relocated		
No	5,450	96
Yes	233	4
Death among relatives and friends		
No	5,575	98
Yes	108	2
Working remotely		
No	2,137	38
Yes	3,546	62
Children		
No	3,387	60
Yes	2,296	40

Their provenience was northern Italy (23%), central Italy (55%), and southern Italy (22%). Only 4% moved to another city as a result of COVID-19 and 62% were able to work remotely. Because data were collected during the first week after the Italian government decreed highly restrictive norms for all inhabitants, only 34% of participants reported being on lockdown for 2 weeks or more. A small percentage of participants endorsed being diagnosed with COVID-19 (6%, $N = 329$) or experiencing the death of close relatives or friends due to the virus (2%, $N = 108$).

Measures

Participants provided socio-demographic information, the presence/absence of positive cases or deaths among relatives and friends, and whether they had moved to another location due to COVID-19. Psychological distress, post-traumatic symptoms, and implicit emotion regulation were assessed using Italian validated version of the Symptom Checklist-90, the Impact of Event Scale-Revised, and the Defense Mechanisms Rating Scales-Self-Report-30, respectively.

The *Symptom Checklist-90* (SCL-90) (29) is a 90-item 5-point scale assessing psychopathological and somatic symptoms occurring during the past week. The SCL-90 provides a Global Severity Index (GSI) and nine subscale scores for psychiatric symptoms, such as somatization, obsessive compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. We focused on the subscales for depression (DEP) and anxiety (ANX) as well as the summary Global Severity Index (GSI). Validity and reliability of the scale are well-documented (30, 31).

The *Impact of Event Scale-Revised* (IES-R) (32) is a 22-item scale assessing the presence of post-traumatic symptoms. The IES-R provides an overall index of PTSS with three subscales reflecting intrusion, avoidance, and hyperarousal. The IES-R has performed well as a screening instrument for PTSD, and has demonstrated concurrent and discriminant validity, as well as a lack of social desirability effects (33).

The *Defense Mechanisms Rating Scales-Self-Report-30* (DMRS-SR-30) (34) is a 30-item questionnaire assessing the whole hierarchy of defense mechanisms (35). The DMRS-SR-30 items were extracted from the observer-rated Defense Mechanisms Rating Scales Q-sort version (DMRS-Q) (36) for use in self-report. The DMRS-SR-30 provides scores for the overall defensive functioning (ODF) and for seven hierarchically ordered defense levels. The defense levels (and constituent defenses), from least to most adaptive are: action (acting out, passive aggression, and help-rejecting complaining), major image-distorting (splitting of self and others' images, and projective identification), disavowal (denial, rationalization, projection, and autistic fantasy), major image-distorting (idealization of self and others' images, devaluation of self and others' images, and omnipotence), neurotic (repression, dissociation, reaction formation, and displacement), obsessive (undoing, intellectualization, and isolation of affects), high-adaptive (affiliation, altruism, anticipation, humor, self-assertion, self-observation, sublimation, and suppression). Preliminary analysis of reliability showed very good internal consistency for ODF (Cronbach's alpha = .890), whereas defense level subscales ranged from .360 to .703 (34). Similarly, very good criterion, concurrent, convergent and discriminant validity for ODF and moderate to high for defense levels subscales (34).

Procedures

This cross-sectional study used snowball sampling *via* social media (e.g., Facebook, Instagram, Twitter) within Italy for data collection. An online survey about the psychological impact of quarantine for COVID-19 outbreak was launched on March 13, 2020 and data was collected for five days, during the first week of the Italian government lockdown decree. Considering the difficulty in enrolling participants under such restrictive measures, we opted for an Internet-based snowball sampling to collect self-report of how the COVID-19 affected participants. The high rate of response (0.0001% of Italian permanent residents of all ages) and the sample stratification by age and region provided an overall picture of the early psychological reaction to the COVID-19 pandemic and associated quarantining. Eligibility criteria for participation was: 1) consent to data being used for research purposes; 2) 18 years or older; and 3) living in Italy during the COVID-19 lockdown. All procedures followed the ethical standards of the Helsinki Declaration and were approved by the institutional review board at University of Pisa.

Statistical Analyses

Stepwise linear regression was used to predict mental health symptoms (GSI and IES) by COVID-19 exposure and demographic variables. Exposure to COVID-19 was calculated as a percentage, with the daily incidence of positive cases in each of 20 Italian regions divided by the total of confirmed COVID-19 cases in Italy, on the day the participant completed the survey (data extracted from Italian Ministry of Health website: https://bit.ly/3dB7t3r). To predict PTSS by COVID-19 exposure, demographics, and overall defense functioning (ODF), stepwise logistic regression was used. Participants were also asked, "Do you have any of your relatives or friends who tested positive to COVID-19?" Responses to this question were classified as "having positive cases nearby" and it was treated as a categorial variable. The stepwise selection method had variable entering criteria of 15% and stay criteria of 5% significance level of the Wald chi-square. To evaluate the impact of defense mechanisms (i.e., implicit emotion regulation), ODF and DMRS-SR-30 subscales were tested as moderators using multivariate linear regression.

RESULTS

Exposure to COVID-19 among participants was 6.4% ($SD = 11.7\%$) on average. Psychological distress was, on average, within the normal range, with GSI and IES-R mean scores ($M = 0.72$, $SD = 0.53$ and $M = 24.72$, $SD = 16.10$, respectively) below the cut-off for psychopathology. Within this sample, 35.6% reported clinically significant levels of distress, measured by the GSI, 29.4% reported clinically significant symptoms of post-traumatic stress, as measured by the IES-R. According to literature, cutoff scores for

clinical significance were GSI > 0.8, IES-R > 33, DEP > 1.04, and ANX > 0.68 (37–39). Significant symptoms of depression and anxiety were reported by 37.8 and 51.1% of participants respectively. Overall defensive functioning fell in the healthy-neurotic range, comparable to a normative community sample (M = 5.7; SD = 0.70) (40). Participants with IES-R scores falling in the PTSD range showed significantly lower ODF (M = 5.21; SD = 0.62; p = .000) and GSI (M = 1.24; SD = 0.53; p = .000).

Results of linear regression are displayed in **Table 2** and indicated that COVID-19 exposure was not a significant predictor of symptoms. However, having positive cases nearby, more days on lockdown, and having to move because of COVID-19 were related to higher symptoms. Older age, working from home, male gender, and not living with close relatives were related to lower symptoms. Findings remained the same when treating age as a continuous variable.

Table 3 shows findings concerning the second hypothesis suggest that the likelihood of developing PTSD increased significantly for ages 30–39 (OR = 1.22) and 40–49 (OR = 1.35) compared to age <30, and decreases by 48% for age > 60, compared to age <30. Females (OR = 2.72) and participants who have positive cases nearby (OR = 1.44) show higher likelihood of PTSD. Higher ODF values are related to decreased likelihood of PTSD. Each increase of one unit of ODF results in a decreased the chance of developing PTSD in 71% (OR = 0.29, p < 0.001).

Table 4 displays the correlations between the defense variables and both overall psychological distress (GSI), depression (DEP), anxiety (ANX), and PTSD symptoms (IES-R). Overall defensive functioning (ODF) was significantly negatively related to symptom levels on all measures, in particular with overall distress and depression. Conversely, all lower/immature defense levels were positively related to symptom levels. Of the defense categories, mature defenses were negatively correlated with symptom scales, whereas neurotic and immature categories were positively associated with psychological distress and symptoms. In descending order of magnitude, they were: depression, anxiety, and PTSD symptoms. The immature defense category displayed the largest positive association to symptoms levels, of which the subgroup of depressive defenses showed the higher correlation compared to non-depressive defenses.

There was a significant moderation effect only for obsessional defenses, for both GSI (β = 0.01, ΔR^2 = 0.0008, p = 0.026) and IES-R (β = 0.43, ΔR^2 = 0.0016, p = 0.002). As illustrated in **Figures 1**, **2**, the strength of the relationship between the number of positive coronavirus cases nearby and GSI or IES-R increases

TABLE 2 | Linear regression for demographic variables predicting distress (N = 5,682).

	Psychological distress (GSI)		PTSD symptoms (IES-R)	
	SE	β	***SE***	β
Age				
< 30				
30–39	0.021	−0.094***	0.595	−0.960
40–49	0.024	−0.133***	0.613	−1.144*
50–59	0.026	−0.216***	0.631	−3.396***
>= 60	0.030	−0.302***	0.751	−7.005***
Female	0.016	0.185***	0.477	8.379***
Living with				
Close relatives				
Alone	0.023	−0.022	0.660	−1.394**
Partner	0.022	−0.088***	0.635	−1.481**
Roommates	0.034	0.047	1.020	−0.011
Close positive cases			0.883	2.165**
Lockdown duration				
<=7 days				
8–14 days	0.015	0.052***	0.470	1.299***
>14 days	0.029	0.139***	0.878	2.775***
Moved to new location	0.034	0.090***		
Working remotely	0.014	−0.045***	0.438	−1.233***
Children	0.020	−0.051**		
Constant	0.020	0.723***	0.617	20.616***
R^2		0.084		0.080
Adjusted R^2		0.082		0.078

*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$, two-tailed.

TABLE 3 | Comparison of parameters and association with post-traumatic stress disorder (PTSD) symptoms.

	No PTSD (IES-R<33) (*N* = 4,012)	PTSD (IES-R >= 33) (*N* = 1,671)	*p*
Age			<0.001
<30	1,280 (31.9%)	655 (39.2%)	
30–39	808 (20.1%)	371 (22.2%)	
40–49	712 (17.8%)	320 (19.2%)	
50–59	707 (17.6%)	247 (14.8%)	
>=60	504 (12.6%)	78 (4.67%)	
Gender			<0.001
Female	2,803 (69.9%)	1,453 (87.0%)	
Male	1,209 (30.1%)	218 (13.0%)	
Relocated			0.013
No	3,865 (96.3%)	1,585 (94.9%)	
Yes	147 (3.66%)	86 (5.15%)	
Living with			0.033
Alone	497 (12.4%)	163 (9.75%)	
Close relatives	2,826 (70.4%)	1,197 (71.6%)	
Partner/lover	516 (12.9%)	230 (13.8%)	
Roommates	173 (4.31%)	81 (4.85%)	
Close positive cases			0.010
No	3,801 (94.7%)	1,553 (92.9%)	
Yes	211 (5.26%)	118 (7.06%)	
Close death			0.038
No	3,946 (98.4%)	1,629 (97.5%)	
Yes	66 (1.65%)	42 (2.51%)	
Lockdown days			0.008
<=7	2,702 (67.3%)	1,070 (64.0%)	
8–14	1,090 (27.2%)	478 (28.6%)	
> 14	220 (5.48%)	123 (7.36%)	
Working remotely			0.667
No	1,501 (37.4%)	636 (38.1%)	
Yes	2,511 (62.6%)	1,035 (61.9%)	
Children			<0.001
No	2,315 (57.7%)	1,072 (64.2%)	
Yes	1,697 (42.3%)	599 (35.8%)	
GSI	0.50 (0.35)	1.24 (0.53)	<0.001
ODF	5.77 (0.71)	5.22 (0.61)	<0.001
COVID-19_impact	6.51 (12.0)	6.10 (10.8)	0.212

TABLE 4 | Pearson correlations between psychological distress, post-traumatic stress disorder (PTSD), and defense mechanisms.

	Overall distress (GSI)	Depression (DEP SCL-90)	Anxiety (ANX SCL-90)	PTSD (IES-R)
ODF	–.506*	–.441*	–.381*	–.341*
Defense levels				
High-adaptive	–.563*	–.490*	–.431*	–412*
Obsessional	.151*	.138*	.118*	.129*
Neurotic	.320*	.281*	.262*	.290*
Hysterical	.335*	.286*	.260*	.260*
Other neurotic	.151*	.138*	.135*	.135*
Minor I-D	.206*	.156*	.135*	.134*
Disavowal	.306*	.270*	.253*	.266*
Major I-D	.549*	.498*	.419*	.348*
Action	.369*	.320*	.279*	.238*
Defense categories				
Mature	–.563*	–.490*	–.431*	–431*
Neurotic	.309*	.275*	.249*	.275*
Immature	.569*	.494*	.434*	.399*
Depressive	.597*	.531*	.449*	.377*
Other immature	.208*	.161*	.167*	.205*

*$p < .001$; image distortion abbreviated I-D.

with the level of obsessional mechanisms. The Johnson-Neyman technique revealed that the relationship between positive coronavirus cases nearby and GSI was significant for all values of obsessional mechanisms above 8.06%, but not significant for values below 8.06%. The relationship between positive coronavirus cases nearby and IES-R was significant for levels of obsessional mechanisms above 6.71%.

DISCUSSION

The present study is timely in view of recent recommendations to assess effects on individual and population mental health during the COVID-19 pandemic (2). While the mean distress scores in this sample were not elevated, a sizable proportion still scored within clinical ranges for overall distress (35.6%), depression (37.8%), anxiety (51.1%), and PTSD (29.4%), indicating significant psychological distress across all domains assessed. Because of our sampling method we do not know if this generalizes to the whole Italian population, which includes people who do not use social media, but the significant proportion of this sample that was in distress makes understanding the correlates meaningful. Similarly, our findings revealed important associations between sociodemographic variables and risk factors for endorsing post-traumatic psychological distress during the COVID-19 pandemic and identified key implicit emotion regulation processes that might moderate this distress. Defenses on every level of the hierarchy were significantly associated with the report of PTSS, positively or negatively. Italians experienced varying levels of distress during the first week of lockdown, depending on their age, gender, lifestyle, traumatic experience related to the virus spread, and defensive functioning.

With regard to the first hypothesis, that some individuals would be at higher risk of psychological distress than others, results confirmed previous findings that younger age and female gender increased the risk of mental health problems (5). This is instructive with regard to COVID-19 given that older individuals are at greater risk of mortality. Interestingly, COVID-19 exposure was not a significant predictor of psychopathology, whereas having positive cases nearby, more days on lockdown,

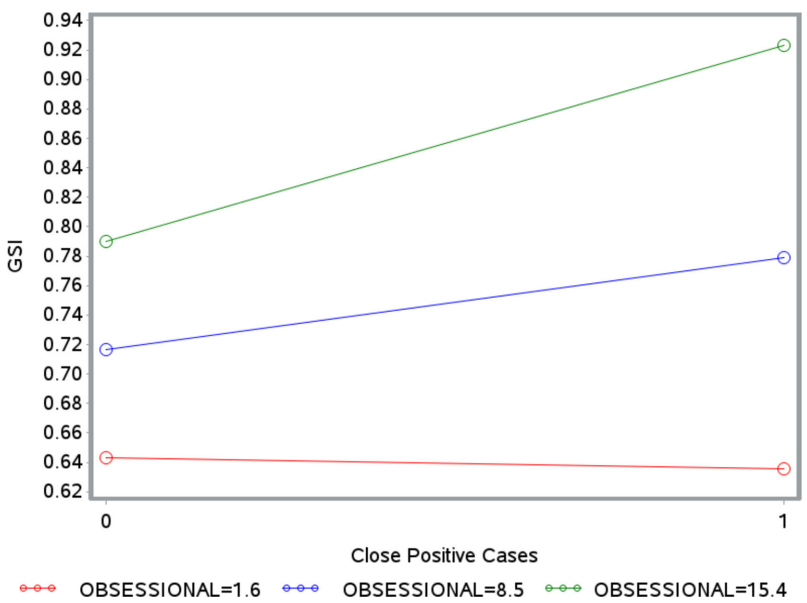

FIGURE 1 | Moderating effect of obsessional defenses on the association between close positive cases and Global Severity Index (GSI). The number 0 on the x-axis indicates the absence of close positive cases. The number 1 on the x-axis indicates the presence of close positive cases. The label OBSESSIONAL refers to defense mechanisms belonging to the obsessional defense level. The red line, blue line, and green line indicate values of obsessional defense level of 1.6, 8.06, and 15.4%, respectively.

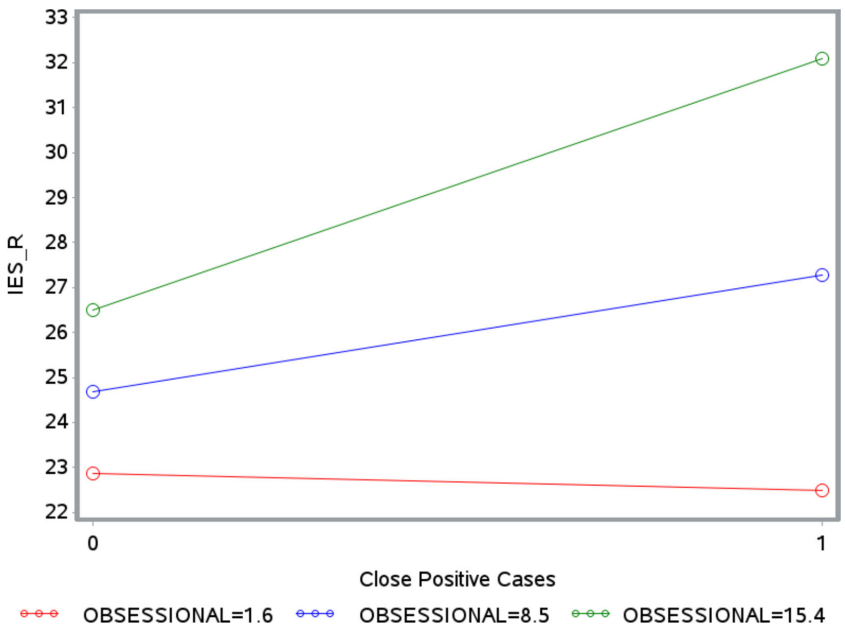

FIGURE 2 | Moderating effect of obsessional defenses on the association between close positive cases and Impact of Event Scale-Revised (IES-R). The number 0 on the x-axis indicates the absence of close positive cases. The number 1 on the x-axis indicates the presence of close positive cases. The label OBSESSIONAL refers to defense mechanisms belonging to the obsessional defense level. The red line, blue line, and green line indicate values of obsessional defense level of 1.6, 8.06, and 15.4%, respectively.

and having to relocate because of COVID-19 were all related to higher levels of distress.

According to research on the psychological impact of COVID-19 (4), we interpreted these findings to indicate that having symptoms was more associated with disruptions and a sense of threat related to the outbreak than living in a region highly hit by the COVID-19.

The second hypothesis, that implicit emotion regulation capacities (e.g., defense mechanisms) would be associated with the risk for PTSD, was fully confirmed. Higher levels of defensive functioning (ODF) were associated with lower levels of overall psychological distress, particularly depressive and anxiety symptoms, and PTSD, sharing respectively 25.60 and 11.63% of the variance. Specifically, the likelihood of having PTSD increased 71% for each unit decrease in ODF. Our findings are consistent with reports that the defense hierarchy is highly associated with measures of symptoms and functioning (41–43). Furthermore when defenses change, symptoms and functioning change in predictable ways (44, 45). As the current pandemic leads to more cases and greater time in lockdown, individual defensive functioning may slip and distress increase. This suggests the importance of considering the use of interventions that foster adaptive implicit emotion regulation (46–48).

Findings confirm that different defense levels are associated with varying levels of adaption to stressors and, hence, overall distress, depression, anxiety, and post-traumatic symptoms. Mature defenses generally accomplish this without distorting reality, while allowing the awareness of personal wishes, fears, and emotional responses, thereby optimizing adapting. Lower defense levels involve some tradeoffs that lead to degrees of poorer adaptation. In order to avoid conflictual motives or feelings, other neurotic defenses hide some important aspect of ideas, motives or feelings, trading off awareness of problems for nameless anxiety. Minor image-distorting defenses temporarily up-regulate self-esteem and sense of adequacy by distorting the images of others or oneself, but without effect on stressors. Disavowal defense deny, cover-up, or mis-attribute the sources of stress to avoid shame and responsibility. Major-image-distorting defenses distort reality into all good or bad images to avoid threats and powerlessness, but failing to see all sides of problems. Action defenses bypass inhibitions and express motives and emotions immediately without considering unpalatable consequences. Finally, the group of depressive defenses showed the strongest positive association to the measures of distress, specifically depression and anxiety, and of PTSD symptoms, consistent with other studies (44, 45).

Consistent with other research (49), moderation analyses found that higher levels of obsessional defenses were associated with increasing distress and trauma symptoms among individuals who know COVID-19 cases. Because obsessional defenses keep facts undistorted, they do not impair functioning; however, by minimizing affective experience, they lead to failures to address one's emotional life and leave the individual vulnerable to distress, as found in other studies (35, 45, 50).

Finally, impaired handling of emotional responses to the COVID-19 disruptions and threats may be associated with the PTSD symptoms of avoidance and hyperarousal. While not

addressed in this report, professional interventions with individuals who are avoiding charged feelings about the COVID-19 outbreak may mitigate the development or exacerbation of PTSD symptoms among those at risk. We also await the replication of our findings in other geographic areas and especially with longitudinal data to examine evidence that any improvements in defensive functioning among those at risk may be associated with diminished distress and trauma symptoms.

This survey used a snowball sampling method *via* social media contacts, which is not systematic but haphazard, and possibly biased in some ways. However, the large number of respondents reflected all Italian regions and a wide range of ages. As a cross-sectional study, causal relationships cannot be determined, nor the sequence in which factors operate. For instance, higher defensive functioning prior to the outbreak should protect individuals from developing symptoms once the outbreak occurred, but this study cannot establish temporality. It could also be that individuals who endorse symptoms during the outbreak tend to score lower on defensive functioning as an effect of self-report while distressed.

Despite its limitations, this study has relevant clinical implications. Findings indicate that defensive functioning, an operationalization of implicit emotion regulation, likely has an impact on the experience of pandemic-associated distress. These mechanisms appear to moderate the relationship between other risk factors—such as knowing someone with COVID-19—and symptoms of distress and PTSD. The key role of implicit emotion regulation in dealing with stressful life events is particularly important for vulnerable people, such as patients with chronic physical and mental illness (51–56).

CONCLUSION

The world is experiencing one of the worst pandemics in recent history with daily exponential increases in diagnosis and mortality. Mental health professionals are observing the psychological impact of such a disaster and are trying to respond with adjusted interventions (57–60). In line with Brooks and colleagues (5), these findings suggest that psychological impact of COVID-19 and associated quarantining must be seriously considered by the healthcare system, with particular attention to those in high-risk categories. Automatic capacities for emotion regulation (e.g., defense mechanisms) may moderate the deleterious effects of pandemic-related trauma (61, 62). Mental health professions may need to screen for poorer defensive functioning in the face of high levels of subjective distress, especially depressive and anxiety symptoms, and PTSD symptoms to provide targeted interventions in order to alleviate distress (63–65).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Committee on Bioethics of the University of Pisa. The patients/participants provided written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MG conceived the research study. MG, CC, and GO created the online survey. MG and JP developed and validated the novel DMRS-SR-30 measure. SZ-M performed data analyses. TP, SZ-M and MG wrote the first draft of the manuscript. JP contributed to the interpretation of the results and critically reviewed the final draft of the manuscript. All authors contributed to the article and approved the submitted version.

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OPINION
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Regulation-Focused Psychotherapy for Children (RFP-C): Advances in the Treatment of ADHD and ODD in Childhood and Adolescence

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INTRODUCTION

Externalizing behaviors are among the most common problems of childhood and affect many aspects of psychological development (Wilens et al., 2002; Liu, 2004). Children with oppositional defiant disorder (ODD) are at higher risk for developing emotional disorders as well as conduct disorder and antisocial personality disorder in adulthood, especially when they receive inadequate psychological support (Rutter et al., 2006; Stringaris and Goodman, 2009; Diamantopoulou et al., 2010; Reef et al., 2010; Hudson et al., 2018).

Parental stress, depression, and anxiety are elevated among parents of children with ODD as compared to those with typical developmental patterns (Katzmann et al., 2018; Lin et al., 2019; Manti et al., 2019). For many years, behavioral parent training (BPT) approaches, including Parent Management Training (PMT), have been the primary treatment option for children with ODD because of their robust evidence base for children with externalizing behaviors (Serketich and Dumas, 1996; Brestan and Eyberg, 1998; Kazdin and Weisz, 1998). All BPT interventions rely on traditional cognitive behavioral strategies in working primarily with the parent, and include behavioral modeling, rewards, reinforcement, and developmentally-appropriate consequences for misbehavior (Webster-Stratton, 1994; Eyberg and Bussing, 2010). A limitation associated with behavioral parent programs is elevated attrition rates for vulnerable populations affected by factors, such as low socioeconomic status, ethnic minority status, low parental functioning, high maternal stress, low parental motivation, and high child symptom severity (Kazdin, 1990; Werba et al., 2006; Fernandez and Eyberg, 2009; Lanier et al., 2011; Granero et al., 2015). Attrition in behavioral parent training may also be due to common parental attributions about where the problem resides—within the child (Baden and Howe, 1992; Bickett et al., 1996; Prout et al., 2015). Parents may feel that since the treatment approach is through the parents, they are implicitly responsible for the child's maladaptive behavior, and may avoid sustained engagement in the treatment to unburden themselves of heightened feelings of responsibility or blame. Finally, behavioral approaches usually do not directly identify, address, or engage with the underlying emotions in the child, which can become dysregulated. An inability to effectively address and engage with these emotions can lead to persistent oppositional behaviors.

In recent years, L.H., T.R., and T.A.P. developed a novel, manualized, time-limited psychodynamic treatment approach for children who present with disruptive behaviors and emotional dysregulation named Regulation-Focused Psychotherapy for Children (RFP-C; Hoffman and Rice, 2016). RFP-C conceptualizes children's externalizing behaviors as expressions of

maladaptive defense mechanisms formulated as the products of developmental delays in the implicit emotion regulation system (Rice and Hoffman, 2014). RFP-C targets the strengthening of the child's implicit emotional regulation system through direct work on the child's maladaptive defenses and provides psychoeducation and empathic support to parents of the child in distress. Throughout 16 individual play therapy sessions and four parent meetings, the clinician increases understanding that all behavior, especially disruptive behavior, has meaning in the service of emotional and behavioral regulation (Prout et al., 2019a). This insight leads to a decreased need and reliance to act on the distressing emotions (e.g., less need for disruptive behaviors) and an increased ability to tolerate, work through, and talk about the feelings that previously needed to be warded off. In addition, parents are relieved of the burden of feeling heightened responsibility as the locus of the child's problems. The clinician joins the parent and the child as a system all directly working toward improvement. The efficacy of RFP-C has been demonstrated in an initial pilot study (Prout et al., 2019b) and promising preliminary data from a recent randomized controlled trial of the intervention (Di Giuseppe et al., 2020c; Prout, 2020).

ASSESSMENT OF DEFENSE MECHANISMS IN CHILDREN

Defined as unconscious operations that protect the self from the awareness of feelings and thoughts of internal conflicts and external stressors (Vaillant, 1992; MacGregor and Olson, 2005; American Psychiatric Association, 2013), defense mechanisms play a key role in RFP-C. This therapeutic approach is based on the observation, interpretation, and developing awareness of child defense mechanisms either activated "in session" or reported in the patient narratives (Perry et al., 2020). The accuracy of defense mechanism assessment becomes essential for successfully addressing immature defensive patterns and fostering adaptive implicit emotion regulation (Di Giuseppe et al., 2019, 2020a). Despite progress in defense mechanism assessment in adults (Bond et al., 1989; Perry, 1990; Perry and Henry, 2004; Di Giuseppe et al., 2014, 2020b), only a few measures assess defenses in children (Cramer, 1991; Laor et al., 2001; Nimroody et al., 2019). None of these utilize an empirically-derived, observer-rated methodology that can be applied to psychotherapy sessions.

To fill the lack of empirical measures for child defense mechanisms assessment, one of the authors (M.D.G.), developed the Q-sort version of the Perry's Defense Mechanisms Rating Scale (DMRS-Q; Di Giuseppe et al., 2014) for clinical use. Our aim is to create a new computerized observer-rated measure for assessing defense mechanisms in children, the Defense Mechanisms Rating Scale—Q-Sort for Children (DMRS-QC), based on the theoretical background of the DMRS-Q. This will be the first attempt to provide an empirical instrument consistent with the definitions and hierarchical organization of defense mechanisms (Vaillant, 1992; American Psychiatric Association, 1994; Perry and Henry, 2004). Analyzing defense mechanisms in action in RFP-C has the potential to promote identification of the defensive profile of children with disruptive behaviors, as well as the changes that underlie successful RFP-C treatment outcome. The DMRS-QC will provide an effective and easy-to-use measure for examining defense mechanisms in children across a wide range of treatment modalities.

TRAINING IN RFP-C

One of the advantages of RFP-C is the ease with which it can be applied. As any other evidence-based psychotherapy, RFP-C requires a specific training for its reliable use.

The training includes didactic instruction, a competency quiz, and attendance at several supervision sessions. RFP-C therapists learn how to focus on behavioral, non-verbal, verbal, and play disruptions as evidence of defense mechanisms in action. Attention is also paid to the importance of the therapeutic relationship as a vehicle for therapeutic intervention. The recognition of specific defensive patterns and their underlying regulation function during the session allow the RFP-C therapist to efficiently address the implicit emotion regulation strategies and enhance changes in the child overall defensive maturity. Thus, the knowledge of definitions and functions of defense mechanisms is a crucial part of the RFP-C training.

DISCUSSION

Preliminary validation studies on the efficacy of RFP-C in treating ODD children have found that the treatment provides relief from symptoms of ODD and an increase in overall emotion regulation (Prout et al., 2019b; Prout, 2020). In working with parents, therapists help them in observing, reflecting and understanding the triggers which provoke the child's disruptive behavior. Parents can then reflect of more effective ways of addressing the triggers. Working with children who have ODD allows them to find new ways of thinking about their emotions and behaviors as a defensive response to anger, frustration, and fear. Throughout the therapeutic relationship children experience positive social relationships where unpleasant feelings can be thought about and not only acted upon.

Initially formulated in New York City as a collaboration among faculty from three institutions, The New York Psychoanalytic Society and Institute, The Icahn School of Medicine at Mount Sinai, and most importantly at the Ferkauf Graduate School of Psychology where the randomized controlled trial has been conducted, RFP-C is now practiced by many practitioners, who have had various exposures to the principles of RFP-C across the United States. Close collaboration with one of the authors (M.D.G.) has allowed us to expand the dissemination of this manualized psychotherapy to Italy, where the Center for Regulation Focused Psychotherapy for Children will begin to offer official RFP-C training in the near future.

AUTHOR CONTRIBUTIONS

MD conceived the idea and made a significant contribution by drafting the manuscript. All authors critically revised the manuscript and approved the final version to be published.

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The Test-Retest Reliability of Heart Rate Variability and Its Association With Personality Functioning

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Background: Heart rate variability (HRV) is a widely used non-invasive index of emotion regulation ability. The main aim of our study was to investigate the relationship between HRV and level of personality functioning in a clinical sample, most of whom had a personality disorder. Our secondary aim was to examine the test-retest reliability of HRV in our sample as there is a lack of knowledge regarding the test-retest reliability in psychiatric populations. We hypothesized that trait HRV would be negatively associated with impairments of personality functioning.

Method: Thirty-two adults (23 females, mean age = 27) with threshold or subthreshold personality disorders were recruited from two psychiatric outpatient clinics in Norway. Impairment of personality functioning was assessed by the first module of the Structured Clinical Interview for the DSM-5 Alternative Model for Personality Disorders (SCID-5-AMPD-I); Level of Personality Functioning Scale (LPFS). HRV was assessed during resting conditions with spontaneous breathing over three separate days. Trait HRV was calculated by averaging all three HRV assessments. The test-retest reliability of HRV was assessed using intraclass correlations.

Results: Contrary to expected, a positive association between trait HRV and the LPFS Self-direction domain emerged. This was driven by positive associations between the LPFS and HRV at time point 2. Overall, the test-retest reliability of HRV was comparable to previous studies on healthy subjects. However, the reliability coefficients for the first two time points were considerably lower relative to the second and third time points.

Conclusions: We propose that impairment of personality functioning may have increased the proportion of variance in HRV attributed to state relative to trait. This could explain the lower test-retest reliability for the first two time points. The increased test-retest reliability for the last two time points could reflect a habituation to the testing situation and hence, less pronounced influences of state in the second and third time points.

Keywords: heart rate variability, emotion regulation (ER), alternative model for personality disorders (AMPD), personality functioning, test-retest reliability, intraclass correlation, trait/state

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INTRODUCTION

Heart rate variability (HRV) is a non-invasive and widely used marker of cardiac autonomic functioning. The term HRV refers to the temporal fluctuations between successive heart beats caused by respiratory cycles and primarily reflects parasympathetic (vagal) influences on cardiac activity (1). These parasympathetic influences are modulated by the central autonomic network (CAN) consisting of cortical and subcortical regions implicated in the regulation of emotional alertness, reactivity, and recovery (2, 3). Specifically, the CAN integrates a constant flow of internal and external contextual information of threat and safety and uses this to adapt the peripheral physiology (e.g., heart rate) and behavior in accordance to everchanging situational demands (1, 2). Heart rate variability may therefore be viewed as a proxy for the ability of the CAN to regulate emotional alertness, reactivity, and recovery with regards to both timing and magnitude in a given context (2). While high HRV reflects a flexible and dynamic capacity for emotional responding, low HRV on the contrary, reflects a poor integration of contextual information and a rigid adaption of behavior to situational demands.

There is robust evidence for an association between reduced HRV and psychopathology (4). In a meta-analytic comparison of both short and long term indices of resting HRV in a wider range of psychiatric disorders (i.e., mood, anxiety-related, psychotic, and substance dependence disorders) Alvares et al. (5) concluded that HRV was reduced in all patient groups compared to controls. Relatively few HRV studies exist in the field of personality disorders (PD), and most of the existing studies have concentrated on borderline PD. A meta-analytic comparison of resting HRV in individuals with borderline PD and healthy controls included five small studies whereof only two reported statistically significant differences in HRV (6). Combining these studies in the meta-analysis yielded a moderate effect size that was comparable to the findings in other psychiatric disorders (5, 6).

The traditional diagnostic systems for personality disorders have been criticized for lacking validity and reliability due to several reasons such as arbitrary diagnostic thresholds and high comorbidity rates (7, 8). A more fruitful way to move forward might be to focus on dimensions of core aspects of personality pathology, like self-regulation problems and interpersonal difficulties (9). Currently, the most well-known dimensional model is the DSM-5 Alternative Model for Personality Disorders (AMPD, (10)). In this model, dimensional aspects of personality pathology are captured by two criteria; A and B. The A criterion, or Levels Personality Functioning Scale (LPFS), aims at assessing a general severity of personality pathology conceptualized as two major components: problems in self- and interpersonal functioning. These components are specified by four areas of impairment (i.e., Identity, Self-direction, Empathy, and Intimacy), which can be assessed by the Structured Clinical Interview for the DSM-5 Alternative Model of Personality Disorders module I [SCID-5-AMPD-I; (11)]. The LPFS offers a novel approach to diagnosing personality disorders by evaluating these aspects on a severity continuum, ranging from little or no impairment of personality functioning (i.e., healthy, adaptive functioning; Level 0), to some (Level 1), moderate (Level 2), severe (Level 3), and extreme impairment of personality functioning (Level 4). Averaging these scores gives a global severity score of personality pathology, which can be used in clinical decision making or in research. The B criterion of the AMPD includes 25 pathological personality traits, organized within five higher order domains (negative affectivity, detachment, antagonism, disinhibition, and psychoticism).

The inclusion of the LPFS in the DSM-5 has given an impetus to research on the assessment of personality functioning (12), and it is to be expected that psychophysiological research will follow. According to the AMPD, emotional regulation, self-esteem regulation, and other self-regulatory capacities are closely related to interpersonal functioning, like the capacity to understand others' intentions and emotions, and the capacity to engage in close relationships. Thus, regulatory capacities are central in the conceptualization of personality functioning, which points toward HRV as an obvious candidate to study the association between personality functioning and psychophysiology (2).

To the best of our knowledge, the test-retest reliability of HRV has only been investigated in healthy subjects and non-psychiatric clinical populations such as patients with chronic heart failure (13). Consequently, there is a lack of knowledge concerning the temporal stability of HRV in psychiatric populations. Test-retest reliability refers to the temporal stability of an instrument measured over repeated occasions conducted under identical conditions (14). Intraclass correlation coefficient (ICC) is a commonly used statistic to express test-retest reliability. Coefficients above 0.5 are generally considered as moderate test-retest reliability and coefficients above 0.8 as good reliability (14). A systematic review of short-term HRV test-retest reliability studies concluded that HRV assessed during rest had moderate test-retest reliability in healthy adults (13). The highest ICCs ranged between 0.84 and 0.90 for time domain measures and between 0.67 and 0.96 for frequency domain measures (13). Later studies have reported comparable findings (15–18).

Using structural equation modeling and latent state-trait theory, Bertsch et al. (15) quantified the relative proportions of variance in HRV explained by trait and non-trait factors in repeated HRV assessments. As little as 52% of the variance in a single HRV assessment was explained by trait, but this proportion increased to 66% and 75% when aggregating two and three HRV assessments, respectively (15). Non-trait influences consist of situational factors and measurement error. Situational factors refer to variance in HRV that is not explained by stable transsituational factors (i.e., trait), thus comprising state factors. These state influences on HRV arise in part from how the individual interacts with the test situation which may be referred to as person-situation interactions. Guidelines for standardizing and conducting ECG-recordings have been recommended to reduce unsystematic measurement variance in HRV, such as allowing the participants to acclimatize to the testing environment prior to initiating the ECG recordings [e.g., (19)]. However, as individuals differ in their perception and appraisal of a given situation, there will be individual differences

in the extent to which the testing situation could impact each participant. In other words, it is not possible to standardize how each individual interacts with the measurement context. Varying proportions of state variance relative to trait variance across repeated HRV assessments can potentially reduce the test-retest reliability of HRV because only variance explained by trait should be consistent across repeated measurements. As such, person-situation interactions might have implications for the test-retest reliability of HRV. Furthermore, person-situation interactions could be especially relevant in the context of personality disorders where emotional dysregulation is a central feature.

The main aim of this study was to examine the association between trait HRV and level of personality functioning as assessed by the SCID-5-AMPD-I (11) in a heterogeneous clinical sample of non-psychotic patients, most of whom had a personality disorder. We hypothesized that participants with greater impairment of personality functioning would exhibit lower trait HRV. Since knowledge about the test-retest reliability of HRV is a prerequisite for an adequate interpretation of the results, our secondary aim was to investigate the test-retest reliability of HRV in our sample.

METHODS

Participants

Thirty-two participants (23 females) with an age range of 21–41 (mean age = 27) were recruited from psychiatric outpatient departments at Oslo University Hospital and the Hospital in Vestfold, Norway. Most participants ($n = 25$) were recruited from specialized PD treatment units at the Norwegian Network for Personality Disorders (20). Diagnostic exclusion criteria were autism spectrum disorder (ASD) and other pervasive developmental disorders, schizophrenia spectrum disorder, sequelae after brain injury, severe ongoing substance abuse, and intellectual disability. Exclusion criteria for participation in the HRV study were use of beta-blockers and extreme workout (defined as 6–7 days a week). One participant was excluded for having ASD, diagnosed after inclusion in the study, leaving 31 subjects eligible for the study.

The network units in Oslo and Tønsberg offer long-term psychodynamic therapy (2–3 years), combining group and individual therapy. All except one patient were included in the HRV project during the clinical assessment phase or during the interim period between clinical assessment and treatment. One patient was in the third year of treatment. The remaining patients ($n = 6$) were recruited from general outpatient departments and were offered treatment for depression or/and anxiety disorders.

Categorical PD diagnoses were assessed before inclusion in the study by therapists at the clinical units where the participants were recruited from, using the Structured Clinical Interview for DSM-IV Axis II PDs [SCID-II; (21)]. Diagnostic PD information of 29 participants was available. Among these, 24 participants (62%) fulfilled criteria for one or more PDs, including PD not otherwise specified. The most common PD diagnosis was borderline PD (35%), followed by avoidant PD (31%), and PD not otherwise specified (19%). Three other PD diagnoses were represented: paranoid PD (2 patients; 6.5%); dependent PD (2 patients; 6.5%), and obsessive-compulsive PD (one patient; 3.2%). Fourteen participants had one PD diagnosis and four participants had two or three PD diagnoses.

As with PD diagnoses, symptom disorders were assessed by referring clinicians, using the Mini-International Neuropsychiatric Interview (MINI) for Axis I diagnoses (22). Diagnostic information was available for 29 participants. The mean number of symptom disorders among these 29 participants was 1.8 (SD =1.6, range 0-6). Ninety-one percent had one or more symptom diagnoses, the most common being major depressive disorder (52%), followed by panic disorder (26%), and social phobia (22%).

Information about daily use of psychotropic drugs was available for 26 patients (84%). Among these, one patient used three types of psychotropics; two patients used two types; eight patients used one type, and 16 patients did not use psychotropics (62%). Antidepressants (SSRI or similar) were most commonly used (10 patients), followed by third generation antipsychotics (3 patients). One patient used a central stimulant and one patient a mood stabilizer.

HRV Data Collection and Analysis

Electrocardiography (ECG) was recorded using portable Biopac PM150 hardware. Three active Ag/AgCl electrodes were placed on the participants' chest, using a modified Lead-II configuration: placing the negative electrode on the right clavicle, the positive on the left lowest rib, and the neutral on the right lowest rib. The hardware was connected to a portable computer containing AcqKnowledge software (Biopac-Systems, 2015) where the hardware data was graphically reproduced as a one lead ECG.

All participants were asked to refrain from nicotine and caffeine 2 h prior to the HRV assessments and received an SMS reminder the same day of the measurement. ECG was recorded in a resting state under identical conditions during a 7-min period, for which the participants were left alone in a room and placed in a comfortable chair. The participants were instructed to sit in a comfortable position, move as little as possible while breathing normally, and relax as much as possible. Inter-beat intervals (IBIs) of heart rate were retrieved via AcqKnowledge®.

Data processing and statistical analysis of HRV followed the recommendations by Malik et al. (23) and was carried out using ARTiiFACT software (24), which is based on an error detection algorithm defining individual threshold criteria for erroneously detected interbeat intervals. The data processing followed Kaufmann et al. (24) references of artifact correction by visually inspecting every signal and replacing missing or incorrect IBIs with cubic spline interpolation of neighboring intervals. Out of the 7-min ECG recordings, only the last 5-min periods were used in the data processing to exclude setting-related disturbances (experimenter leaving/entering the room). A criterion threshold was calculated for each individual recording based on the participant's distribution of IBIs to allow for further efficient identification of measurement artifacts. Erroneous beats were deleted and substituted by means of cubic spline interpolation.

Statistical time and frequency domain measures of HRV were obtained via ARTiiFACT. The root of the mean squared successive differences of R-R-intervals (RMSSD) was used as a time domain measure, and absolute high frequency (HF; 0.15–0.40 Hz) was obtained as a measure in the frequency domain. The selection of HRV indices followed recommendations by Task Force guidelines and common research practice (2, 23, 25–27).

Each participant underwent between one and three HRV assessments on separate days. Thirty-one subjects participated in the first assessment, 26 subjects participated in two out of three assessments and 18 subjects participated in all three assessments. The lower participation in the subsequent time points was due to drop-out. The measurement intervals could not be standardized due to practical reasons and were scheduled individually with each participant. The measurement intervals ranged between 1 and 113 days for T1-T2 (mean = 22), and between 1 and 75 days for T2-T3 (mean = 21).

SCID-5-AMPD-I

The Norwegian translation of the first module of the SCID-5-AMPD-I (28) was used to assess impairment in personality functioning. The SCID-5-AMPD-I closely follows the DSM-5 AMPD, differentiating between the four elements of the LPFS, i.e., Identity and Self-direction (Self), and Empathy and Intimacy (Interpersonal). These elements are operationalized by three indicators each. In more detail, Identity contains Sense of self, Self-esteem, and Emotional dysregulation; Self-direction includes Ability to pursue meaningful goals, Constructive internal standards of behavior, and Self-reflective functioning; Empathy contains Comprehension and appreciation of others' experiences, Tolerance of differing perspectives, and Understanding of one's own behavior on others; and Intimacy comprises Depth and duration of connection with others, Desire and capacity for closeness, and Mutuality of regard reflected in interpersonal behavior. In the SCID-5-AMPD-I, each indicator is scored on a scale from 0 (no impairment) to 4 (severe impairment), and these twelve scores can be used to compute a mean score, reflecting the overall level of impairment in personality functioning, or it can be used to compute mean subscores for the four elements of the LPFS, as was done in this study. A higher score indicates more severe impairment in personality functioning.

In more detail, the SCID-5-AMPD-I starts the assessment of personality functioning by posing eight general questions to obtain a global impression of the interviewee's level of personality functioning. After these initial questions, the twelve indicators of the LPFS are assessed separately by a combination of screener questions and questions for level determination, resulting in a score varying from 0 to 4 for each indicator. Based on the interviewee's responses to these screener questions and the responses to the eight preliminary questions, the interviewer conducts a preliminary evaluation of the level at which the interviewee may be functioning, and proceeds by posing determination questions pertaining to that level. The interviewer continues to pose questions corresponding to increasing levels of impairment, until the interviewee clearly does not qualify for that level of impairment, which would imply a score just beneath that level. If none of these levels are applicable, the interviewer carries on posing questions at the level just beneath the lowest level already assessed and continues in descending order. By the end of the interview, the overall level of personality functioning is computed by dividing the total score by 12.

The SCID-5-AMPD-I was administered prior to the HRV recordings by experienced clinicians trained by Donna Bender at a two-day workshop. See Buer Christensen et al. (29) for detailed information about this training. A dual-design interrater reliability study (a video-based design and a test-retest design) conducted by the current research group found excellent intraclass correlation coefficients for both the global LPFS scores and the scores of the four elements of the LPFS (29). The participants were included in the HRV study after the administration of the SCID-5-AMPD-I. However, detailed information about the time lapse between the SCID-5-AMPD-I and the first HRV measurement is not available.

Statistical Analysis

The statistical analyses were performed using SPSS version 25 for Windows. All variables were checked for univariate outliers and normality prior to analysis. The trait HRV variable was computed by averaging the HRV assessments of all three time points. Calculating the mean of repeated HRV assessments is an alternative way of increasing the relative proportion of trait variance without using structural equation modeling (30). For those participants who could not participate for the third HRV assessment, only the two first assessments were used. The results from the analyses are reported for both time (RMSSD) and high frequency (HF_{power}) domains.

The RMSSD variables had no outlying cases and were normally distributed. The HF_{power} at T1, 2, and 3 were logarithmized (log10) to achieve normal distributions. There were no outlying scores across the LPFS domain variables.

Three intraclass correlation coefficients (ICC) based on the 3,1 formula (i.e., 2-way mixed-effects model, single measures) with absolute agreement were calculated to evaluate the test-retest reliability of the HRV assessments (31, 32). One ICC was calculated for all three HRV assessments to determine the overall test-retest reliability of the HRV assessments. Two additional ICCs were subsequently computed; one for the first and second HRV assessments and one for the second and third assessments.

RESULTS

The descriptive statistics are presented in **Table 1**. Mean LPFS was 2.0. As the threshold for a PD is at level 2 in the LPFS, this is in accordance to the observation that most participants in the sample had a PD. The results of test-retest reliability analyses are presented in **Table 2**. For all three measurement occasions (T1+T2+T3), the ICCs indicate good test-retest reliability, both for RMSSD and HF_{power} (0.70 and 0.67, respectively). However, the ICC estimates from T1 to T2 were considerably lower (0.50 and 0.51, respectively), representing fair agreement. It should be noted that the 95% confidence intervals were rather broad for the

TABLE 1 | Descriptive statistics.

	n	*M (SD)*	Range
Age	31	27.0 (4.2)	21.0–41.0
LPFS			
Identity	31	2.4 (0.8)	0.0–3.3
Self-direction	31	2.0 (0.9)	0.0–3.3
Empathy	31	1.6 (1.0)	0.0–3.3
Intimacy	31	2.1 (1.1)	0.0–3.7
Total	31	2.0 (0.9)	0.0–3.3
RMSSD			
T1	31	47.3 (20.5)	11.8–97.3
T2	26	47.9 (22.3)	18.9–95.7
T3	18	43.8 (24.6)	8.5–88.6
Mean	26	46.3 (18.4)	13.8–81.2
HF_{power} log10			
T1	31	1,004 (731)	46–3,261
T2	26	1,283 (1,318)	102–5,813
T3	18	775 (750)	40–3,018
Mean	26	1,045 (840)	155–3,927

M, mean; SD, standard deviation; LPFS, Level of personality functioning scale; RMSSD, root mean square of successive differences; HF, high frequency; T, time point.

TABLE 2 | Intraclass correlations for HRV.

HRV index	HRV time points	ICC (3,1)
RMSSD	1+2+3 ($n = 18$)	0.70 [0.47–0.86]
	1+2 ($n = 26$)	0.50 [0.15–0.74]
	2+3 ($n = 18$)	0.80 [0.54–0.92]
HF_{power} log10	1+2+3 ($n = 18$)	0.67 [0.43–0.85]
	1+2 ($n = 26$)	0.51 [0.16–0.74]
	2+3 ($n = 18$)	0.64 [0.28–0.85]

95% Confidence intervals in brackets. HRV, heart rate variability; ICC, intraclass correlation; RMSSD, root mean square of successive differences; HF, high frequency.

ICCs from T1 to T2, which can be explained by the moderate sample size in combination with large intra-individual variation from T1 to T2. Thus, there is large uncertainty in the estimation of the ICCs from T1 to T2.

To account for the possible confounding effects of drop-out, the ICC analyses were repeated in the 18 subjects that underwent all three ECG-recordings. The estimated ICCs revealed a similar pattern of lower test-retest reliability in T1+T2 compared to T2+T3. For RMSSD, ICC for HRV T1+T2 was ICC = 0.58, 95% CIs = 0.12-0.82, $p = 0.005$, and for HRV T2+T3 ICC = 0.80, 95% CIs = 0.54-0.92, $p < 0.001$. For HF_{power}, ICC for HRV T1+T2 was ICC = 0.55, 95% CIs = 0.12-0.81, $p = 0.009$, and for HRV T2+T3, ICC = 0.64, 95% CIs = 0.28-0.85, $p = 0.001$. Overall ICCs (i.e., T1+T2+T3) for RMSSD was ICC = 0.70, 95% CIs = 0.47-0.86, $p < 0.001$, and for HF_{power} was ICC = 0.67, 95% CIs = 0.43-0.85, $p < 0.001$.

The results from the correlation analyses between HRV and the LPFS are presented in **Table 3**. At T1, the correlations between HRV and personality functioning were negative or around zero, both for RMSSD and HF_{power}. At T2, these correlations were positive, and for several LPFS domains the correlations emerged as statistically significant. Specifically, for RMSSD at T2, statistically significant associations emerged for all LPFS domains except the Intimacy domain. The correlation between HRV T2 and LPFS total score and the Identity domain showed tendencies toward positive associations ($p = 0.076$ and $p = 0.079$, respectively). At T3, no statistically significant associations emerged, but there was an overall pattern of positive associations. Among these associations, RMSSD at T3 showed a tendency toward a positive association with the Self-direction domain ($p = 0.059$).

TABLE 3 | Pearson correlations between HRV indices and LPFS domains.

HRV index	LPFS	HRV T1 ($n = 31$)	HRV T2 ($n = 26$)	HRV T3 ($n = 18$)	HRV mean ($n = 26$)
RMSSD	Mean LPFS	−0.121	0.448*	0.353	0.361
	Identity	−0.222	0.408*	0.257	0.270
	Self-direction	−0.051	0.503**	0.453	0.452*
	Empathy	−0.206	0.438*	0.311	0.313
	Intimacy	0.016	0.249	0.175	0.234
HF_{power} log10	Mean LPFS	−0.089	0.355	0.332	0.345
	Identity	−0.262	0.350	0.250	0.203
	Self-direction	−0.021	0.428*	0.399	0.419*
	Empathy	−0.138	0.297	0.234	0.284
	Intimacy	0.058	0.201	0.224	0.275

**sig at the .05-level. **sig at the .01-level. HRV, heart rate variability; LPFS, level of personality functioning scale; T, time point; RMSSD, root mean square of successive differences; HF, high frequency.*

For mean HRV, an overall pattern of positive associations was observed with the LPFS domains, but only the association between mean HRV and Self-direction was statistically significant. In addition, mean HRV and the LPFS total score had a tendency toward a positive association in both RMSSD and HF_{power} ($p = 0.070$ and $p = 0.084$, respectively). These findings suggest that higher trait HRV was associated with higher scores on the LPFS, i.e., more impairment of personality functioning.

DISCUSSION

The present study investigated the associations between HRV and level of personality functioning as assessed with the SCID-5-AMPD-I. To the best of our knowledge, this is the first study to explore the relationship between HRV and personality functioning in accordance with the DSM-5 AMPD, and to assess the temporal stability of HRV in a psychiatric sample. Contrary to expected, there was a positive relationship between impairment in personality functioning and trait HRV (i.e., mean HRV over all three time points). This was driven by the positive associations between HRV at T2 and the LPFS domains. The estimated ICCs for the three HRV assessments indicated good test-retest reliability in both time and frequency domains, but the ICCs

for the first two time points (T1 and T2) were considerably lower, representing fair reliability. In both the time and frequency domains, the ICCs were higher for T2+T3 compared to the ICCs for T1+T2.

As low HRV is considered as a transdiagnostic vulnerability marker for psychopathology (4), the positive associations between trait HRV and the LPFS Self-direction subscale, along with the positive associations between HRV T2 and the LPFS subscales were unexpected. A meta-analysis of resting vagal tone in individuals with borderline PD concluded that these individuals had lowered vagally-mediated HRV (6). A possible explanation for this discrepancy could be that the studies included in the meta-analysis were based on single HRV assessments. The non-significant negative correlations between HRV at T1 and the LPFS Identity and Empathy subdomains support this position. In their meta-analysis, Koenig et al. (6) point out that three out of the five included studies did not observe significant effect sizes, possibly due to lack of power. As such, although not significant, the small negative effect sizes for HRV at T1 and the LPFS Identity and Empathy subdomains may be considered in line with previous HRV research in borderline PD.

Thus, though there might be an association between low HRV and personality pathology, this association seems to be smaller in PDs than in symptom disorders. Our study even suggests that there might be no association or even a positive association between the general severity of PD and HRV. A possible explanation could be that PDs in a larger degree are influenced by psychosocial factors as compared with symptom disorders. More precisely, that PDs contain aspects that have developed under the influence of environmental factors and aspects that are based on biological factors. In fact, the inclusion of both the A (personality functioning) and B criterion (personality traits) in the DSM-5 AMPD reflects a possible differentiation between psychosocial and biological influences in the development of PDs. This assertion parallels modern conceptualizations of normal personality, which discerns between basic tendencies and characteristic adaptations (33, 34). Basic tendencies are assumed to be biologically based and are represented by the "Big Five" of normal personality, (i.e., Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness) and has its pathological counterpart in the trait model of the AMPD. Characteristic adaptations, on the other hand, include attitudes, motives, goals, values, self-images, mental representations of significant others, and many other aspects of human individuality that are shaped by social experience. It is these aspects of personality the LPFS was designed to capture. As such, biologically based measures, including HRV, might be less sensitive to capture impairment in personality functioning according to DSM-5 since these characteristics are assumed to be more influenced by psychosocial processes than by basic biological processes. This hypothesis should be examined more extensively in future psychophysiological studies on the DSM-5 AMPD including the A criterion as well as the B criterion.

Our estimated ICCs for T2+T3 and T1+T2+T3 were comparable to previous short-term test-retest reliability studies in healthy individuals with spontaneous respiration [e.g., (13, 15, 18)]. The ICCs for T1+T2, on the contrary, were lower than in previous studies. Most studies differ in the number of days between each time point (1–210 days) but have generally reported similar test-retest reliabilities of around ICC = 0.70 (13, 15, 17, 18). As our estimated ICCs were in line with previous test-retest reliability studies in healthy individuals, it is unlikely that the variable days between each time point in our study could have confounded the test-retest reliability. This is in line with a systematic review concluding that HRV assessments recorded sequentially and 6 months apart are similarly reliable (13). In line with this, Cipryan and Litschmannova (16) did not standardize the number of days between each time point, where the two first time points occurred directly after each other while the third time point was two to 30 days after the first ECG recording. They reported ICC = 0.93 (HF_{power}) for T1+T2 and ICC = 0.78 (HF_{power}) for T1+T3 which is in line with previous studies using standardized intervals between time points.

Previous research has shown that up to 48% of the variance in a single HRV assessment is explained by non-trait influences such as affective states during the time of assessment (15). By aggregating repeated HRV assessments, Bertsch et al. (15) reduced non-trait influences down to 25%. Although existing guidelines for standardizing the testing environment are followed (e.g., 18), it is not possible to standardize how the individual interacts within the testing situation. This has implications for the test-retest reliability of HRV because state inherently varies across repeated measurements. As individuals with personality disorders are associated with difficulties in self and self-other representations (9) and a larger volatility of vagal activation (6) it is plausible that the state influences on HRV were exacerbated on T1 relative to T2 and T3. Our findings of relatively low ICCs for T1+T2 with an increased reliability for T2+T3 may reflect greater proportions of state relative to trait influences on the variance in T1. A major difference between T1 and the subsequent time points was the novelty of the testing situation in T1, which may have invoked greater affective responses in some participants in T1 relative to the subsequent time points. The results from the ICC analyses where the subjects that dropped out were excluded, precludes drop-out as a confounding factor in these findings. Taken together, we suggest that lower personality functioning lends the individual more vulnerable to novel situations, which in turn could exacerbate state influences on HRV, thus reducing trait variance and consequently compromising the test-retest reliability of HRV.

The findings of the present study must be viewed in light of some limitations. The moderate sample size could have contributed to type II errors. This also prevented us from considering potential confounding variables in the analyses. We therefore think that our findings should be considered as preliminary. As highlighted by Koenig et al. (6), both pharmacological and psychological treatment can have an impact on HRV. However, the effect of most types seems to be small, except for tricyclic antidepressants and clozapine (5). The majority of our sample did not use any psychotropic medication, and none used tricyclic antidepressants or clozapine. We neither deem it likely that psychological treatment had substantial effect on the results since the intervals between HRV measurements were small for most cases, and psychodynamic therapy targets long-term personality change, not immediate

symptom reduction. Due to practical limitations, it was not possible to standardize the number of days between each HRV assessment in our study. However, previous test-retest reliability studies have differed in the amount of elapsed time between each assessment, and there is not convincing evidence that different time intervals affect the test-retest reliability of HRV (13). We did not assess the participants' affective states (e.g., perceived stress, anxiety, or depressive symptoms) during the HRV assessments, which we would recommend for future studies. Explicitly assessing the participants' affective states during the ECG-recordings could contribute with insight about how person-situation interactions might affect the test-retest reliability of HRV. Lastly, we did not control for habitual smoking or BMI. Despite considerable inconsistencies between HRV measures and assessment conditions, there are indications of small statistical effects of both BMI and habitual smoking on short-term HRV recordings under resting conditions [e.g., (35, 36)].

CONCLUSIONS

Contrary to our hypothesis, impairment in personality functioning was not associated with reduced trait HRV. This discrepancy with previous studies could be explained by the fact that we measured HRV at several points, and that HRV increased substantially from the first to the second time point. Our findings show that the reliability of HRV assessed at rest with spontaneous breathing in individuals with personality disorders is comparable to previous test-retest reliability studies in healthy adults. However, the relatively low estimated ICCs for the first and second time points suggest that a higher degree of state factors compromised the reliability of the first HRV assessment. These state factors could possibly have been exacerbated by impairment in personality functioning.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because this will require a more thorough anonymization of the data and an approval by the Security officer at Oslo University Hospital. We welcome any request for the data and are open to initiate this process if necessary. Requests to access the datasets should be directed to Fillip Ferreira Eikeseth, fillip.ferreira.eikeseth@regionh.dk.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Regional Committee for Medical and Health Research Ethics (REK; Reference 2015/1900/REK Sørøst). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FFE and BH: design, data collection, data analysis and manuscript preparation. SSS and BRB: design, data collection and manuscript preparation. IU-M: data collection and manuscript preparation. SSS: design, data analysis and manuscript preparation. All authors contributed to the article and approved the submitted version.

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REVIEW
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Effects of Neurological Disorders on Bone Health

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Neurological diseases, particularly in the context of aging, have serious impacts on quality of life and can negatively affect bone health. The brain-bone axis is critically important for skeletal metabolism, sensory innervation, and endocrine cross-talk between these organs. This review discusses current evidence for the cellular and molecular mechanisms by which various neurological disease categories, including autoimmune, developmental, dementia-related, movement, neuromuscular, stroke, trauma, and psychological, impart changes in bone homeostasis and mass, as well as fracture risk. Likewise, how bone may affect neurological function is discussed. Gaining a better understanding of brain-bone interactions, particularly in patients with underlying neurological disorders, may lead to development of novel therapies and discovery of shared risk factors, as well as highlight the need for broad, whole-health clinical approaches toward treatment.

Keywords: Neurology, disease, osteoporosis, bone, mental health, depression, PTSD

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INTRODUCTION

The skeleton is necessary for facilitating movement, providing a framework for muscles and soft tissues, protecting vital organs, storage of minerals and fat, harboring the bone marrow, and regulating blood cell formation. Maintaining bone health is, therefore, important for overall health and well-being. In recent years, we have begun to better dissect the relationship between the brain and skeleton and how they regulate one another. One way to better appreciate this relationship is to determine how it becomes altered with disease. Osteoporosis is the most common form of metabolic bone disease and is characterized by low bone mass ($\leq$ 2.5 standard deviations below peak bone mass) and micro-architectural bone deterioration that can lead to debilitating fractures. In the United States, osteoporosis accounts for over 1.5 million fractures annually. By 2050, the costs associated with osteoporotic fractures are expected to exceed $130 billion (Bartl and Bartl, 2019). In regard to brain disease, more than one million U.S. adults are diagnosed annually with a chronic brain disease or disorder at a healthcare cost of $>$ $800 billion (Gooch et al., 2017). In addition, many of these disorders are associated with increased age, a shared risk factor with osteoporosis. Osteoporosis is more prevalent in people with neurological conditions, such as multiple sclerosis (MS) and Parkinson's disease (PD), while sudden neurological events, such as stroke and spinal cord injury (SCI), can cause rapid loss in bone mineral density (BMD). Further, lack of physical activity in degenerative neurological conditions can lead to mineral loss and osteoporosis, particularly in aging populations and/or those with comorbidities (e.g., obesity, diabetes, smoking). A better understanding of the mechanisms that cause bone loss and how neurological conditions uniquely impact bone health is of clinical importance and will guide

treatment options, encourage lifestyle change, and aid in development of novel osteoporosis therapies. Likewise, gaining a better understanding of how bones regulate the brain may provide novel insights into how neurological disorders develop. This review will provide an overview of literature related to neurological disorders and their effects on bone health with a goal to promote recognition of the mechanisms by which changes in the brain can impart changes in the bones. We also discuss how certain treatments for neurological disorders can negatively affect bone health. This will encourage a broader view of disease management toward improved patient health and outcomes.

BONE-BRAIN INTERFACE

As an adaptation to stress and to maintain calcium homeostasis, the skeleton undergoes constant remodeling. In adult humans, the skeleton replaces itself almost entirely every 10 years [Office of the Surgeon General (US), 2004]. During this remodeling process, the new bone laid down by osteoblasts must replace the bone resorbed by osteoclasts in a fine-tuned manner. However, with age, net bone loss occurs as a result of increased osteoclastic activity and/or decreased osteoblastic activity at a rate of approximately 1% per year after 30 years of age. The bone remodeling process is regulated by endocrine, paracrine, mechanical, and, as the subject of more recent focus, neuronal factors.

Investigation into the contribution of neuronal signaling in regulating bone remodeling and homeostasis began with a focus on leptin, an adipose-derived hormone involved in energy regulation and metabolism. Mice deficient for leptin (*ob/ob* mice) were found to have a high vertebral trabecular bone mass phenotype (Ducy et al., 2000). This phenotype was, surprisingly, rescued by infusion of small amounts of leptin in the third hypothalamic ventricle (Thomas et al., 1999; Cornish et al., 2002; Takeda et al., 2002). It became evident that the pathways connecting brain and bone play critical roles in energy regulation and bone metabolism. Since this landmark finding, a rapid expansion in studies attempting to understanding this brain-bone interface occurred, with both the sympathetic (SNS) and parasympathetic nervous systems (PNS) having now been shown to regulate bone through various pathways, including leptin, serotonin, adiponectin, circadian genes, neuropeptide Y, muscarinic receptors, nicotinic receptors, beta-adrenergic receptors, and sensory nerve innervation of bone (Marenzana and Chenu, 2008; Dimitri and Rosen, 2017; Elefteriou, 2018). The importance of autonomic tone in regulating bone mass is supported by the observed benefit of beta-blockers on BMD and fracture risk (Schlienger et al., 2004; Bonnet et al., 2007; Graham et al., 2008; Reid, 2008).

Psychological stress can also impart changes in bone. We have previously discussed the relationship between osteoporosis and psychological stress, which is partially regulated through activation of the hypothalamic-pituitary-adrenal (HPA) axis, glucocorticoid signaling, and blunted response of growth factors that contribute to bone mass, such as insulin-like growth factor-1 (IGF-1) (Kelly et al., 2019). Conversely, bone has been found to regulate the brain, with osteocalcin (OCN), an osteogenic hormone, being essential for activation of the acute stress response via inhibition of the PNS (Berger et al., 2019). Thus, the brain-bone axis is critically important for skeletal metabolism, sensory innervation, and endocrine cross-talk between these organs.

Low BMD and cognitive impairment/reduced executive function often occur together, with osteoporosis and related fracture being associated with progression of cognitive impairment, likely, in part, due to increased fall risk (Liu-Ambrose et al., 2007; Cauley et al., 2016). In community-dwelling adults aged > 50 years without history of stroke or dementia, low BMD correlated with cognitive impairment, even after adjusting for confounding factors (Kang et al., 2018). Cognitive impulsivity is significantly related to BMD in elderly women, while verbal working memory has been associated with BMD and may alter fracture risk (Martino et al., 2019; Catalano et al., 2020b). The incidence of physical frailty and dementia follow similar patterns in the aging population, providing further evidence that frailty and cognitive function may be mechanistically and pathologically linked (Halil et al., 2015). Possible mechanisms for the association between BMD and cognitive impairment have been proposed. Mineral concentrations in osteoporosis may facilitate formation of senile plaques and neurofibrillary tangles (NFT) in Alzheimer's disease (AD) (Lopez et al., 2008; Loskutova et al., 2009; Zhou et al., 2011). Estrogen, involved in bone homeostasis, may also affect cognitive function through inhibition of neuronal apoptosis, promotion of synaptic plasticity, reduction of oxidative stress, and improvement in cerebral blood flow by increasing high-density lipoprotein cholesterol levels (Funk et al., 1991; Brownbill and Ilich, 2004; Zhou et al., 2011; Kang et al., 2018). Further, estrogen replacement may lead to benefits in cognitive function (Luine, 2014). Age-related alterations in inflammatory processes, including increased levels of circulating IL-6 and diminished T regulatory cell activity, may dually contribute to bone loss (via local activation of osteoclasts) and cognitive decline (via increasing levels of neuronal α2-macroglobulin, a protease inhibitor implicated in AD plaques) (Ershler, 1993; Licastro et al., 2000; Lui et al., 2003). Lastly, parathyroid hormone (PTH) may represent a clinically important link between cognitive dysfunction and bone health, as a regulator of calcium and phosphate metabolism that can cross the blood-brain barrier (Lourida et al., 2015; Murthy et al., 2018). Hyperparathyroidism has been associated with physical frailty, bone mass loss via osteoclast activation, as well as poor cognitive function, potentially through calcium overload, disruption of neuronal signaling, and hippocampal atrophy (Numann et al., 1984; Roman et al., 2005; Marcocci et al., 2012; Murthy et al., 2018). It is clear that the bone and brain play key roles in regulating each other. Understanding how bone phenotypes are altered with neurological disorders may provide further mechanistic insights.

NEUROLOGICAL DISORDERS

To date, there are more than 600 classified neurological disorders with distinct etiology, neuro-pathophysiology,

and symptomology. Herein, we discuss major categories of neurological disorders, including autoimmune, dementia-related, infection-related, movement-related, neural developmental, neuromuscular, psychological, trauma-related, vascular, and other neuronal diseases. Although the etiology of many neurological disorders is highly complex and not fully understood, genetic, epigenetic, and external (e.g., trauma, infection, environment) factors have been implicated in neurological disease initiation and progression. Considerable clinical evidence across many neurological disease categories indicates that changes in neurophysiology lead to changes in bone physiology, resulting in decreased BMD and bone mineral content (BMC), altered bone microarchitecture, and decreased bone strength, ultimately leading to the development of osteopenia/osteoporosis and increased fracture risk. Recent clinical and preclinical studies have begun to shed light on some of the shared hormonal, immune, and molecular/cellular pathways that are impacted in neurological disorders and may mediate secondary effects in bone (**Table 1**). These include sustained activation of peripheral and central nervous systems (CNS), inflammatory pathways, changes in glutamate signaling, dysregulation of the SNS and PNS, and HPA axis dysregulation. In addition to shared pathophysiology, lifestyle changes secondary to neurological disorders, including modifications in diet and overall physical activity, can contribute to deleterious bone effects. Further, drug treatments for many neurological disorders (e.g., selective serotonin reuptake inhibitors (SSRIs), antipsychotics, anti-epilepsy drugs) have independent and overlapping roles in mediating bone loss. Since osteopenia/osteoporosis and resulting fracture have debilitating effects on patient quality-of-life, it is imperative that we understand how neurological diseases lead to secondary effects in bone to move toward more informed, comprehensive clinical treatment.

Autoimmune Disorders

Multiple Sclerosis

Multiple sclerosis is the most common, non-traumatic disease impacting young adults and can be divided into two stages: an inflammatory phase leading to relapsing-remitting disease and a secondary phase leading to prolonged neurodegeneration and non-relapsing, progressive disease (Dobson and Giovannoni, 2019). Early disease is characterized by neural inflammation, leading to the production of demyelinating plaques in the CNS that results in episodes of vision loss, fatigue, and tingling/numbness. As MS progresses, irreversible axon damage occurs and patients experience pain, muscle spasms, vision loss,

TABLE 1 | Neurological disorders, impacts on bone, and potential mechanisms.

Neurological Disorder	Impact on Bone		Potential Molecular/Cellular Drivers
	↓ BMD	↑ Fracture Risk	
Acute Spinal Cord Injury	✓	✓	CGRP, OPG, PTH, RANKL, Vasoregulation, VIP, Vitamin D, Wnt
Alzheimer's Disease	✓	✓	Aβ, ApoE, Calcium, Collagen, ERK, GPR158/OCN, IκB-α, OPG, OPN, PNS signaling, RANKL, Serotoninergic input, SOST, TREM2, Wnt/β-catenin
Amyotrophic Lateral Sclerosis	✓	✓	Akt, β-catenin, Calcium, Erk1/2, Neurotoxic metals, RANKL, SOST, Vitamin D
Ataxia	✓	✓	Frataxin, Immune dysregulation, Vitamin D
Autism Spectrum Disorder	✓	✓	IGF-1, OCN, Prolactin, Vitamin D
Cerebral palsy	✓	✓	Calcium, IGF-1, PTH, SOST
Chronic Fatigue	✓	✓	IGF-1, Macrophages, MALP-2
Epilepsy	✓	✓	ALP, BALP, Calcium, Collagen, OCN, PTH Sodium, Vitamin D
Major Depressive Disorder	✓	✓	ACTH, Calcium, IL-1β, IL-2, IL-6, Leptin, OPG, OPN, PTH, RANKL, SNS signaling, TNF-α, Vitamin D
Multiple Sclerosis	✓	✓	IL-1, IL-6, IL-11, IL-17A, OPN, PNS signaling, PTH, SNS signaling, TNF-α, Vitamin D
Myasthenia Gravis	✓	✓	Acetylcholine, Vitamin D
Neuromuscular Dystrophy	✓	✓	Calcium, Dystrophin, IL-6, IL-11, Inhibin-βA, OCN, OSX, RANKL, SMN1/2, TGFβ2, Vitamin D
Parkinson's Disease	✓	✓	Homocysteine, Lewy body deposition, PTH, Vitamin D
Post-Traumatic Stress Disorder	✓	✓	β-adrenergic stimulation, Catecholamines, Glucocorticoid signaling, IGF-1, IL-1β, IL-6, NF-kB, RANK/RANKL, TNF-α
Sepsis/SAE	✓	?	Collagen, Macrophages, Monocyte precursors, Myelopoiesis
Sleep Disorders	✓	?	Cortisol, CRP, CTX, Hypoxic signaling, IL-6, P1NP, TNF-α, Vitamin D
Stroke	✓	✓	Estrogen, Neuroinflammation, OPG, Vitamin D
Substance Abuse Disorder	✓	✓	ALP, BALP, BGP, LDL, Leptin, Vitamin D
Traumatic Brain Injury	✓	✓	Calcium, Collagen, IGF-1, NF-κB, OCN, PTH, Vitamin D
Vertigo	✓	✓	Calcium, Estrogen, SNS signaling, Vitamin D

Neurological disorders are associated with negative impacts on bone. These effects may be mediated by primary pathophysiology, lifestyle changes as a result of neurological disease, and first- and second-line therapies. Clinically supported evidence of impacts on BMD and/or fracture risk are marked by "✓." Unknown or understudied effects are noted by "?." Molecular/cellular targets and signaling pathways implicated in mediating effects on bone are listed for each disorder.

and trouble walking. While the etiology of MS has not been fully elucidated, it likely involves multiple factors in addition to genetic predeterminants, including smoking, vitamin D, obesity, gut microbiota, and Epstein-Barr virus (EBV) infection (Dobson et al., 2012; Michel, 2018).

Clinical evidence suggests that MS is associated with detrimental bone effects, including osteopenia/osteoporosis and increased fracture risk (Moen et al., 2011; Sioka et al., 2011; Coskun Benlidayi et al., 2015; Huang et al., 2015a; Bisson et al., 2019). Meta-analyses show that MS patients have reduced BMD in lumbar spine, femur neck, and hip regions compared to healthy controls (Huang et al., 2015a). In a large clinical study, the prevalence of osteoporosis was found to be significantly higher in MS patients (16–26%) compared to healthy controls (6–15%) after adjusting for potential confounding factors, including age, sex, previous fracture history, and comorbidities (Bisson et al., 2019). Assessment of bone microarchitecture in MS patients, reported as a trabecular bone score (TBS), revealed no significant changes compared to healthy controls, suggesting that bone density, but not microarchitecture, is impacted in MS (Olsson et al., 2018).

Potential risk factors for reduced BMD in MS patients include vitamin D insufficiency, disease duration (> 7 years), total steroid dose (> 15 g), disease severity, decreased ambulation, altered parasympathetic signaling, and inflammation (Coskun Benlidayi et al., 2015; Huang et al., 2015b; Murphy et al., 2016). In female MS patients, BMD of lumbar spine and femoral neck was found to be 1-2 SDs lower than in age-matched, healthy controls, with lowest BMD values observed in patients with most severe disease (Nieves et al., 1994). BMD was directly correlated to levels of circulating vitamin D and inversely correlated with levels of parathyroid hormone (PTH), pointing to vitamin D deficiency and hyperparathyroidism as potential contributors to bone loss. In another study of both female (pre- and post-menopausal) and male MS patients, significant bone loss was observed in the femoral neck region, with female patients also presenting with bone loss in the spine. Compared to 2% of healthy controls, 22% of these patients had experienced a non-trauma-related fracture since the age of 35, highlighting a significant clinical outcome (Cosman et al., 1998). Both ambulatory status and steroid treatment > 5 months were shown to be predictors of bone loss, and patients with low levels of vitamin D exhibited greater bone loss overall. Importantly, bone loss in the spine was only observed in patients with low vitamin D levels and was insignificant in patients with normal vitamin D levels. In relatively young, ambulatory patients experiencing acute MS relapses, 51% were found to have low BMD and 62% were found to be vitamin D-deficient, providing further support for a potential link between bone health and vitamin D status (Murphy et al., 2016).

Disease severity and duration, as well as decreased ambulation, have been associated with bone loss and increased risk of fracture in MS patients (Tyblova et al., 2015; Olsson et al., 2018). MS patients with moderate disease, defined by a score of < 4.5–6.5 > on the Expanded Disability Status Scale (EDSS), had lower BMC and BMD in total and regional scans compared to patients with mild disease (score < 1.0–4.0 >) (Pilutti and Motl, 2019). In studies of pre-menopausal women with MS, a significant inverse relationship was observed between EDSS score, disease duration, and BMD, also pointing to disease severity as a primary predictor of bone loss (Zorzon et al., 2005; Terzi et al., 2010). Importantly, lifetime dosage of glucocorticoids was not associated with bone loss in this population, but only with EDSS score (Zorzon et al., 2005). In male patients, decreased mobility and lower EDSS scores were associated with decreased BMD in the femur and muscle wasting in the lower extremities (Zikán et al., 2012). Chronic use of glucocorticoids was not associated with bone loss in this population.

Inflammation has been implicated as a driver in MS-related bone loss. Several inflammatory factors implicated in the pathogenesis of MS, including IL-1, IL-17A, TNF-α, IL-6, and IL-11, have been shown to play a role in osteoporosis (Rifas, 1999; Kasper and Shoemaker, 2010). Levels of proinflammatory osteopontin (OPN) are increased in MS patients compared to healthy controls, with levels directly correlating with femur neck bone loss (Altıntaş et al., 2009). In relapsing-remitting MS patients, increased levels of circulating OPN were shown to correlate with levels of circulating IgG and markers of bone turnover, pointing to OPN as a potential driver of MS-related bone loss (Vogt et al., 2010). Increased levels of OPN were also observed in the cerebrospinal fluid (CSF) of MS patients and correlate with cognitive impairment, suggesting OPN may be a key player in the dysregulated bone-brain axis in MS and may serve as a biomarker of disease progression (Wen et al., 2012). In addition to pathological inflammatory processes, alterations in SNS and PNS signaling have been observed in MS patients and, in some cases, correlate with disease severity and progression (Flachenecker et al., 1999, 2001; Elefteriou, 2008). In a cross-sectional study, patients with active relapsing-remitting MS exhibited impaired sympathetic function and decreased levels of circulating catecholamines compared to healthy control and clinically stable patients (Bartl and Bartl, 2019). Longitudinal follow-up of a subset of these patients revealed a progressive decline in parasympathetic, but not sympathetic, function, suggesting that autonomic tone is differentially impacted as the disease progresses. Future studies in MS patients will be required to delineate the direct and indirect impacts of autonomic dysfunction on bone, as well as how bone innervation and/or signaling may change with disease progression. Together, these studies indicate that pathological mechanisms mediating primary MS symptoms and impaired mobility play major roles in mediating bone loss in MS patients, while the effects of glucocorticoids on bone in MS may be minimal and potentially offset by the positive impact of restored mobility.

Dementia

Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder and the primary cause of dementia. AD currently affects over 5.8 million Americans age 65 and older, and this is anticipated to grow to 13.8 million by mid-century (Alzheimer's Association, 2020). AD is characterized by progressive loss of cognitive function and pathologically by extracellular senile

plaques enriched in amyloid-β peptide (Aβ) and intracellular NFTs formed by hyperphosphorylated tau protein (Mandelkow and Mandelkow, 2012; Selkoe et al., 2012). For over 20 years, skeletal fragility has been recognized as a comorbidity in AD (Birge et al., 1994; Melton et al., 1994; Johansson and Skoog, 1996; Weller, 2004; Looker et al., 2012). Low BMD and osteoporosis occur at twice the rate in AD patients as neurotypical adults, and this is independent of age, sex, body mass index, physical activity, and disease stage (Melton et al., 1994; Weller, 2004; Loskutova et al., 2009; Zhou et al., 2011, 2014; Zhao et al., 2012). Bone loss has been shown to occur in pre-clinical AD, often preceding diagnosis, thus it may have predictive value in estimating AD risk and likelihood of progression to full AD in patients with mild cognitive impairment (MCI) (Tan et al., 2005; Zhou et al., 2011, 2014; Chang et al., 2014; Sohrabi et al., 2015). Low BMD values have been suggested to predict a faster and more severe rate of cognitive decline (Zhou et al., 2014). Thus, while bone loss cannot be used as an independent risk factor for AD, as it frequently occurs in the non-dementia population, it may add predictive value to models used to assess dementia risk.

Regarding molecular pathways that intersect brain and bone in AD, the major genetic risk factor for AD is the apolipoprotein E (ApoE) 4 allele (Raber et al., 2004). ApoE also plays a critical role in maintaining bone mass by promoting osteogenesis and inhibiting osteoclastogenesis (Noguchi et al., 2018). Transgenic mouse models of AD, including the htau, amyloid precursor protein (APP)/presenilin1 mutant, and Swedish mutation APP strains exhibit low BMD (Cui et al., 2011; Yang et al., 2011; Xia et al., 2013; Peng et al., 2014; Dengler-Crish et al., 2016). Studies using the htau mouse model showed evidence of low BMD that preceded the onset of widespread tauopathy and memory deficits (Dengler-Crish et al., 2016, 2018). Tauopathy in the dorsal raphe nucleus (DRN) localized within serotonergic neurons and was associated with a 70% reduction in the overall number of serotonergic neurons in htau DNR, suggesting a link between serotoninergic input, bone loss, and AD. In AD mouse models that overexpress Aβ (e.g., *APPswe* and *APP/PS1ΔE9*), low BMD and osteoporosis were reported (Yang et al., 2011; Zhou et al., 2014). APP and its cleavage fragment Aβ are expressed in both neural and non-neural tissues, including osteoblasts and osteoclasts, and studies show that Aβ can directly impair osteoblast proliferation and promote osteoclast activity (Cui et al., 2011; Xia et al., 2013). Mechanistically, Aβ was shown to enhance RANKL-induced osteoclast activation through IκB-α degradation, ERK phosphorylation, and calcium oscillation signaling pathways (Li et al., 2014).

Clinical evidence suggests that dysfunctional autonomic signaling contributes to AD-related bone loss. AD patients commonly exhibit increased sympathetic tone and reduced parasympathetic flow, marked by reduced cholinergic innervation in the aging population (Aharon-Peretz et al., 1992; de Vilhena Toledo and Junqueira, 2010; Schliebs and Arendt, 2011). Further, AD patients treated with AChE inhibitors exhibit reduced risk of hip fracture and improved bone healing, suggesting that impaired parasympathetic signaling impacts bone homeostasis in AD patients and may be targeted to improve bone health (Weller, 2004; Tamimi et al., 2012; Eimar et al., 2013).

A potential common contributor to both AD and bone loss is the wingless-type murine-mammary-tumor virus integration site (Wnt) signaling pathway. In brain, Wnt signaling plays a role in neuronal survival and formation of synaptic connections and has been reported to play a neuroprotective role in AD (Oliva et al., 2013). In bone, Wnt signaling through the canonical (i.e., Wnt/β-catenin) pathway promotes osteoblast differentiation and increased bone mass (Krishnan, 2006). Mechanistically, this pathway influences renewal of stem cells, stimulation of pre-osteoblast replication, induction of osteoblastogenesis, and inhibition of osteoblast and osteocyte apoptosis (Krishnan, 2006). Loss-of-function mutations in the Wnt signaling pathway results in skeletal fragility and decreased bone mass (Shah et al., 2015). Preclinical studies in the htau mouse demonstrated Wnt signaling deficiencies in both the brain and bones of mice with low BMD (Dengler-Crish et al., 2018). Triggering receptor expressed on myeloid cells-2 (TREM2) is one potential activator of the canonical Wnt/β-catenin pathway that may tie together bone and brain effects. TREM2 is expressed on microglia, where it is neuroprotective, and on osteoclasts, where it controls the rate of osteoclastogenesis (Otero et al., 2012; Jay et al., 2015; Bemiller et al., 2017). Homozygous loss-of-function mutations in TREM2 are associated with an autosomal recessive form of early-onset dementia presenting with bone cysts and consequent fractures called Nasu–Hakola disease (Paloneva et al., 2000). Meta-analysis has shown heterozygous rare variants in TREM2 are associated with a significant increase in the risk of AD (Guerreiro et al., 2013). Together, these studies suggest a common potential target for addressing bone loss in AD.

While the studies above highlight the potential mechanisms regulating brain's influence on bone, an understanding of bone's effects on brain is emerging. Bone is considered an endocrine organ that influences other organs through the secretion of proteins, such as OCN, sclerostin (SOST), and OPN. Blood biomarkers associated with osteoporosis, including C-terminal collagen fragments, OPG, and OCN, are increased in AD (Emanuele et al., 2004; Luckhaus et al., 2009). OCN is a bone-derived hormone that can regulate brain development and function (Greenhill, 2013). Circulating OCN inversely correlates with age, and cognitive function of aged mice can be improved with injection of plasma from young mice (Villeda et al., 2014). Most recently, Karsenty's group has identified the G protein-coupled receptor 158 (GPR 158) as a receptor for OCN in the brain (Khrimian et al., 2017; Obri et al., 2018).

Sclerostin is an osteocyte-specific secreted glycoprotein, encoded by the SOST gene that binds to low-density lipoprotein-receptor-related protein-5 or -6 (LRP5/6) to regulate Wnt signaling. Through this binding, SOST prevents Wnt ligand binding to LRP5/6 and its co-receptor, Frizzled, leading to decreased bone formation and increased bone resorption (Shah et al., 2015). While these data suggest SOST may impact Wnt signaling, which, in turn, affects the brain and AD pathophysiology (Inestrosa et al., 2002; Inestrosa and Varela-Nallar, 2014), further research needs to be conducted, as it is unclear if circulating SOST can cross the blood-brain

barrier (BBB). One potential mechanism by which SOST could influences brain physiology may be through vascular regulation. SOST has recently been shown to influence vascular pathophysiology, a known risk factor for dementia, with high levels of SOST having been linked to cardiovascular mortality (Justin et al., 2013; Novo-Rodríguez et al., 2013; Catalano et al., 2020a). However, whether or not SOST plays an associative or causative role in vascular pathophysiology, and how this may influence development of dementia, remains unknown.

Osteopontin is thought to enhance bone resorption by anchoring osteoclasts to bone matrix, and high serum levels of OPN correlate with low BMD in post-menopausal women (Reinholt et al., 1990; Cho et al., 2013; Fodor et al., 2013). OPN also acts as a cytokine with upregulated production in response to inflammation and injury, including neuronal damage (Denhardt et al., 2001; Wang and Denhardt, 2008). OPN levels increase in patients with MCI progressing to AD, suggesting OPN could be a marker of neuroinflammation and early clinical stages of AD (Simonsen et al., 2007; Sun et al., 2013). Thus, it is possible that, early on, increased OPN expression may be neuroprotective in AD. This is supported by studies demonstrating a more marked increase in OPN levels in AD subjects in early stages of disease (Comi et al., 2010).

Shared risk factors for AD and bone loss include aging, systemic inflammation, depression, genetics, sex, and physical inactivity. However, the relationship between bone loss and AD is complex and cannot be solely attributed to aging, osteoporosis, or dementia. Rather, data suggest there are common pathophysiological mechanisms contributing to both diseases. Further adding to this complexity is the reciprocal crosstalk that occurs between brain and bone. Thus, bidirectional signaling between brain and bone tissue should be considered in the context of AD and its treatments.

Infection

Septicemia/Sepsis

Septicemia, the entry of bacteria into the bloodstream, leads to rapid immune activation and can result in a systemic reaction (sepsis), which can lead to death (Taeb et al., 2017). While the pathophysiology of sepsis is complex, it involves an impaired immune response in which an initial, rapid increase in inflammation is followed by sustained dysregulation of immune activation/suppression, impacting multiple organ systems and resulting in long-term morbidity (Uhle et al., 2016; Taeb et al., 2017; Cecconi et al., 2018). Increased activation of the peripheral immune system can also lead to CNS inflammation, owing to a disrupted BBB, which can result in sepsis-associated encephalopathy (SAE) (Meneses et al., 2019). As SAE impacts roughly 70% of septic patients and is a leading cause of brain dysfunction, it is critical to understand the mechanisms by which sepsis-induced dysregulation of the neuroimmune-endocrine response may impact organ systems like bone (Lamar, 2011).

Clinical evidence suggests sepsis negatively impacts bone health. In a retrospective study of patients initially treated for sepsis with absolute increase ≥ 2 in Sequential Organ Failure Assessment score, significant bone loss was observed in the thoracic, lumbar, and sacral spine regions (Hongo et al., 2019). A second retrospective study showed that sepsis patients had an increased risk for developing osteoporosis compared to non-sepsis patients (Lee et al., 2020). In addition to bone loss, sepsis has been linked to heterotopic ossification, the abnormal formation of lamellar bone in connective tissue. In a retrospective study of patients hospitalized for burn injuries, sepsis following burn injury was associated with the development of heterotopic ossification ∼37 days after admittance, suggesting sepsis temporally modulates bone physiology (Orchard et al., 2015). Together, these studies indicate that the mechanisms by which sepsis impacts bone are complex and likely dependent on many factors, including type, duration, and location of initial infection.

Studies in preclinical models have shown sepsis rapidly reduces bone strength, impacts cellular differentiation in bone marrow (BM), and induces prolonged changes in peripheral macrophage populations. In a rat model of cecal ligation-puncture, trabecular bone strength was significantly reduced beginning 24 h following sepsis induction and was associated with decreased collagen and mineral elastic modulus at 24- and 96-h post-sepsis induction, respectively. These results suggest sepsis rapidly impacts biomechanical properties of bone and may lead to lasting changes in bone microarchitecture (Puthucheary et al., 2017). In addition to altered biomechanics, data indicate sepsis impacts differentiation of BM myeloid cells. In a combined rodent model of burn injury and sepsis, a shift in myeloid differentiation toward monocytopoiesis 72 h following thermal injury was reported, indicating sepsis can lead to rapid changes in differentiation of HSCs in BM (Santangelo et al., 2001). Alterations in the BM compartment were also observed in a rodent model of cecal ligation-puncture, in which epigenetic modifications in BM-derived monocyte precursors were found to impact the function and wound-healing capabilities of circulating macrophages (Davis et al., 2019). These studies point to modulation of monocyte differentiation and macrophage function as additional mechanisms by which sepsis may induce long-lasting effects in bone, possibly through dysregulated osteoclast differentiation and/or alterations in osteal macrophage function.

Movement Disorders

Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative basal ganglia syndrome characterized by bradykinesia and rigidity, resulting in limited daily activity and increased fall risk (Latt et al., 2009; Tassorelli et al., 2017). A number of studies have examined impacts of PD on bone, with PD being associated with decreased BMD and increased fracture risk (Vaserman, 2005; Wood and Walker, 2005; Fink et al., 2008; Gnädinger et al., 2011; Raglione et al., 2011; van den Bos et al., 2013; Gao et al., 2015; Sleeman et al., 2016). Meta-analysis indicates PD patients are at a higher risk for osteoporosis and have lower hip, lumbar spine, and femoral neck BMD compared to healthy controls (Zhao et al., 2013). Women with PD have 7.3% lower total hip BMD and an increased risk of hip fracture (Schneider et al., 2008). Vitamin D

concentrations and weight loss are reduced in early PD patients and associated with bone loss (van den Bos et al., 2013; Ozturk et al., 2020). No difference was found in BMD between male PD subjects with short disease duration (0 to 5 years) compared to those with longer disease duration (5 to 10 years), suggesting PD progression may not correlate directly to decreasing BMD and that early detection is key to addressing PD-induced bone loss (Daniel et al., 2012). Thus, PD patients should be closely monitored for vitamin D levels and weight, as well as receiving routine dual-energy X-ray absorptiometry (DEXA) scans and fracture risk assessment (FRAX) (Henderson et al., 2019).

Evidence for molecular mechanisms of PD related to bone loss and increased fracture risk is scant. Lewy body deposition in areas of the brain that regulate bone growth and strength may play a role (Litvan et al., 2007; Daniel et al., 2012). Lifestyle changes associated with PD may result in vitamin D deficiency, which can impact bone loss via compensatory hyperparathyroidism (Invernizzi et al., 2009; van den Bos et al., 2013; De Pablo-Fernández et al., 2017). PD also alters levels of bone metabolism markers (Sato et al., 2004; Bezza et al., 2008). Elevated homocysteine levels from levodopa treatment, the central drug treatment for PD, may also impact bone, as homocysteine can induce osteoclast differentiation and osteoblast apoptosis (Koh et al., 2006; Lee et al., 2010). A significant proportion of PD patients suffer from depression, and concomitant use of antidepressants with levodopa results in a 3- to 5-fold increase in risk of hip and femur fracture (Lieberman, 2006; Arbouw et al., 2011). In general, several factors may be involved in development of bone loss associated with PD, including limited mobility/activity, malnutrition, low body mass index, decreased muscle strength, medication use, and vitamin D deficiency (Invernizzi et al., 2009; Malochet-Guinamand et al., 2015). Larger and more powerful studies are needed to determine effects of PD on osteoporosis risk and to stratify this risk by various confounding factors.

Ataxia

Ataxia, a degenerative CNS disease, results in impaired balance and coordination. It is usually caused by damage to the cerebellum but can be caused by damage to the spinal cord or other nerves. There have been few studies on subtypes of ataxia and their effects on bone. In Friedreich ataxia (FDRA), the most common inherited ataxic disorder in the Caucasian population caused by a GAA triplet expansion in the first intron of the frataxin gene on chromosome 9q13, scoliosis and foot deformities are frequent (Labelle et al., 1986; Delatycki et al., 2005; Milbrandt et al., 2008). A strong negative correlation between ataxia severity, GAA repeat length, and BMD was reported in the femoral neck of FDRA patients (Eigentler et al., 2014). The low observed BMD may be due to disease-related falls, mobility restrictions, and/or wheelchair-dependency. Additionally, vitamin D levels were low in the patient cohort, but it is unclear as to why. Suboptimal bone growth and mineralization in FRDA patients during childhood and adolescence may also impact adult BMD and growth. Farias et al. assessed BMD in patients with spinocerebellar ataxia type 3, also known as Machado-Joseph disease (MJD), which is a progressive ataxia resulting in movement restriction caused by an abnormal cytosine-adenine-guanine (CAG) expansion on chromosome 14q32.1. Ten patients out of thirty showed low BMD in at least one of the sites studied, while five patients had at least one lumbar fracture and seven patients reported more than ten falls per month (Farias et al., 2019). This study also found a correlation between CAG expansion and low femoral neck score, providing further evidence that gene alterations may be related to lower BMD. Simonsen et al. found that 75.3% of patients with hereditary ataxia had osteopenia or osteoporosis (Simonsen et al., 2016). These studies suggest the need for routine BMD measurements in ataxia patients to initiate prophylactic osteoporosis treatments. Further studies are needed to determine molecular and genetic mechanisms as opposed to lifestyle changes (e.g., reduced exercise/mobility, increased falls) that may be causing bone loss. In addition, patients with ataxia telangiectasia show immune dysregulation and premature aging, both of which can affect bone loss (Ambrose and Gatti, 2013). Examining immune markers and comparing bones from young ataxia patients to bones from the elderly may provide new pathways for study.

Neural Development Disease

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with heterogeneous origin and symptomology, including atypical autism, autism, and Asperger Syndrome, that disproportionately impacts males (3:1) (Kim et al., 2011; Sinha et al., 2015; Bhandari et al., 2020). Main symptoms include lack of social interaction, abnormal emotional/sensory processing, and repetitive, restricted behaviors, while secondary symptoms can include irritability, anxiety, aggression, and comorbid disorders. The etiology of ASD is complex and likely involves variations in genes regulating synaptogenesis and signaling pathways, as well as epigenetic and environmental factors, that ultimately lead to neural plasticity dysfunction and the precipitation of social, emotional, and sensory processing symptoms.

Poor nutrition, decreased physical activity, vitamin D deficiency, and use of antipsychotic therapies (APTs) have been associated with poor bone health in ASD. In a cross-sectional study of adolescent boys aged 8–17 years, ASD patients exhibited lower BMD in the lumbar spine, femoral neck, total hip, and whole-body regions compared to age-matched controls (Neumeyer et al., 2013). In addition to lower BMD scores, adolescent boys with ASD had lower consumption levels of protein, calcium, and phosphorus, and were less physically active than typically developing adolescents. In another study of prepubertal boys, patients with ASD were shown to have lower BMD at both the hip and femoral neck regions compared to healthy control patients, as well as lower levels of serum vitamin D and decreased physical activity, pointing to vitamin D deficiency and decreased overall activity as potential risk factors for ASD-related bone loss in the adolescent ASD population (Neumeyer et al., 2013).

Autism spectrum disorder also impacts bone microarchitecture and fracture risk. In a cross-sectional study of adolescent boys, ASD patients exhibited lower trabecular

thickness, compressive stiffness, and failure load at the ultradistal radius, as well as a 61% reduction in cortical area compared to typically developing controls, with similar effects observed in the distal tibia (Neumeyer et al., 2017). These ASD patients also exhibited increased body fat, increased serum IGF-1, lower lean mass, and decreased whole body and femoral neck BMD, suggesting physical activity, nutrition, and changes in IGF-1 responsiveness may contribute to ASD-related changes in bone density and microarchitecture. Increased fracture risk has also been observed in the ASD patient population. In a national study of emergency room visits, a higher rate of hip fractures was observed in both children/adolescents (3–22 years) and adults (23–50 years) with ASD compared to patients without ASD, with a higher rate of forearm and spine fractures also observed in adult women (Neumeyer et al., 2015).

While not all studies in the ASD population control for use of APTs, such as risperidone, there is evidence that patients taking APTs have decreased BMD. In a study of adolescent boys with ASD, ∼49% of patients taking an APT had hyperprolactinemia with decreased lumbar spine BMD, as well as decreased levels of the bone turnover marker, carboxyterminal cross-linking telopeptide of bone collagen, compared to patients taking APT without hyperprolactinemia (Roke et al., 2012). Another study of ASD boys aged 5–17 years taking risperidone showed decreased trabecular BMD and decreased radius bone strength compared to healthy controls (Calarge and Schlechte, 2017). Preclinical studies have shed light on the biological mechanisms by which ASD, as well as APT treatment, may impact bone health. In a genetic mouse model for human 15q11-13 duplication, decreased bone mass was observed and associated with osteoblast reduction and decreased bone formation (Lewis et al., 2017). Osteoblasts from ASD mice exhibited decreased proliferation, differentiation, and mineralization, whereas osteoclasts were minimally impacted. In a rat model of ASD, based on maternal exposure to LPS, ASD rats showed decreased bone stiffness and strength, in addition to a reduced number of OCN-positive cells compared to control rats, also indicating that ASD leads to impaired osteoblast proliferation and/or differentiation (Amini et al., 2020). Treatment of ASD rats with risperidone led to more extreme impacts on bone strength, providing evidence that APT treatment exacerbates ASD-related bone effects. Additional studies will help delineate the influence of APTs on bone health in the context of ASD.

Cerebral Palsy

Cerebral palsy (CP) is the most common motor disorder in children and causes a wide range of symptoms impacting neurological (e.g., ataxia, impaired gross motor coordination), orthopedic (e.g., hip dysplasia/dislocation), cognitive (e.g., autism, epilepsy), and visual/hearing systems (Brandenburg et al., 2019; Vitrikas, 2020). CP etiology is complex and involves pathophysiology in the brain and spinal cord. Spastic CP, which accounts for > 80% of cases, is thought to result from dysfunction in the spinal cord, leading to disinhibition of motor neurons and causing symptoms of spasticity, impaired coordination/movement, hyperreflexia, muscle contracture, and weakness (Sheean and McGuire, 2009; Brandenburg et al., 2019). While the pathological development of spastic CP is complex, it has been linked to asphyxia, prenatal/neonatal hemorrhagic or ischemic stroke, infection, brain malformation, trauma, and genetic factors (Brandenburg et al., 2019).

In addition to neuromuscular dysfunction, children and adolescents with CP often present with impaired bone health. Children with quadriplegic CP had reduced BMD of the lumbar spine compared to age-matched healthy children, with the most severe bone impacts observed in patients at level V of the Gross Motor Function Classification System (GMFCS) and in malnourished patients, pointing to disease severity, mobility, and malnutrition as potential risk factors for bone loss (Alvarez Zaragoza et al., 2018). In addition to disease severity, changes in the IGF-1 axis have been implicated in CP-induced bone loss. BMD was significantly decreased in children with spastic CP compared to healthy children and was associated with low circulating IGF-1 levels, severe GMFCS level, and use of anticonvulsive drugs. Children with CP also exhibited increased fracture risk (Nazif et al., 2017).

There is conflicting evidence for the role of anticonvulsive drugs as a risk factor for low BMD. In a study of non-ambulatory children with CP, no significant differences in BMD were found between children taking and not taking anticonvulsant therapies (Cheng et al., 2016). However, nutritional status was implicated as a risk factor. Studies comparing ambulatory and non-ambulatory children with CP have shown that the main predictor of low BMD in the distal femur is impaired mobility (Finbråten et al., 2015). Adolescents and young adults with CP have shown similar deficits in areal BMD, which were associated with reduced mobility by the GMFCS (Trinh et al., 2019).

Although less well-studied, there is clinical evidence that adult CP patients also exhibit bone loss. In a study of premenopausal women and men under 50 years old, BMD was significantly decreased at the lumbar spine, total hip, and femoral neck regions compared to healthy controls. For the lumbar spine and hip, BMD was associated with impaired motor ability by the GMFCS (Fowler et al., 2015). In a demographically similar population, BMD at the second metacarpal bone (mBMD) was found to be decreased and correlated with use of anticonvulsant drugs (Nakano et al., 2003). In men, abnormal calcium metabolism was also associated with lower mBMD, whereas, impaired mobility was associated with mBMD in women, suggesting the mechanisms by which CP impacts bone health may be sex-dependent and include both physical and biomolecular factors. In a study of ambulatory versus non-ambulatory adult CP patients, non-ambulatory patients had decreased BMD, lower PTH levels, and higher SOST levels compared to ambulatory patients, implicating systemic changes in hormones and bone remodeling factors in CP-related bone loss in adult patients (Shin et al., 2017). Taken together, these studies implicate disease severity, mobility status, and alterations in hormones and bone remodeling factors as critical risk factors for CP-associated bone loss.

Epilepsy

Epilepsy is a complex neurological disorder characterized by repeated, unprovoked seizures. Diagnosis is made upon the occurrence of two or more unprovoked seizures more than

24 h apart or one unprovoked seizure with high probability of recurrence (> 60%) over the next 10 years (Beghi et al., 2015). While the etiology of epilepsy is unknown, genetic predisposition, brain injury, and infection have been implicated as causal factors (Thijs et al., 2019). Epilepsy is a highly heterogeneous disorder, with four major types (focal, generalized, combined focal/generalized, and unknown) that can be divided based on nature of seizure onset, as well as level of awareness, motor symptoms, and non-motor symptoms (Thijs et al., 2019).

Patients with epilepsy have increased risk of developing osteoporosis and increased fracture risk that is 2–6 times higher than the general population, independent of seizure-related fractures (Diemar et al., 2019a). Decreased exercise, a more sedentary indoor lifestyle, and use of anti-epileptic drugs (AEDs), which can lead to impaired coordination and disrupted calcium/vitamin D metabolism, may contribute to poor bone health (Kobau et al., 2004; Shellhaas and Joshi, 2010; Diemar et al., 2019b). A meta-analysis of epileptic children showed a significant BMD decrease at lumbar spine, trochanter, femoral neck, and total body regions (Zhang et al., 2015). Decreased serum vitamin D and increased serum alkaline phosphatase (ALP) were also observed, suggesting abnormal vitamin D and/or calcium metabolism may contribute to decreased BMD in children with epilepsy.

Use of AEDs, especially cytochrome P450 enzyme-inducing AEDs (EIAEDs), have been associated with poor bone health in children and adult patients with epilepsy. In ambulant children with epilepsy, use of > 2 EIAEDs was shown to be a significant risk factor for low lumbar BMD (Fong et al., 2018). In a case-control study of matched-pair adolescents, epileptic patients taking AEDs had a significantly increased fracture risk and a 14% reduction in trabecular volumetric BMD compared to matched controls, demonstrating a link between AED use and poor bone health (Simm et al., 2017). A similarly designed study of same-sex twin/age-matched sibling pairs showed EIAED users exhibited a greater reduction in hip and total body BMD, which was not observed in non-enzyme-inducing AED (NEIAED) users, pointing to EIAEDs as the primary driver of bone loss in this patient population (Shiek Ahmad et al., 2017). Similarly, patients on carbamazepine (CBZ), a widely used EIAED, have increased hip and femoral neck BMD loss during initial years of therapy compared to nonusers and have increased hip BMD loss compared to users on NEIAEDs, including levetiracetam and valproate. While the mechanisms by which EIAEDs impact bone have not been fully elucidated, increased catabolism of vitamin D to inactive metabolites, decreased calcium, increased PTH, and increased bone turnover have been implicated (Pack, 2008). In a study of epilepsy patients taking CBZ for > 12 months, decreased BMD and decreased serum vitamin D were observed. A concomitant increase in OCN was observed in CBZ users, suggesting that, in addition to modulation of vitamin D, CBZ may impact bone turnover (Suljic et al., 2018). In an epilepsy rat model, CBZ was associated with decreased serum vitamin D and elevated PTH, as well as decreased BMC, impaired collagen crosslinks, and decreased microhardness, indicating CBZ therapy may affect bone strength and microarchitecture (Garip Ustaoglu et al., 2018). Although less well documented, there is evidence to suggest that some NEIAEDs, including valproate, also impact bone health in patients with epilepsy. In a meta-analysis of valproate users, BMD was found to be decreased in spine and femoral neck regions compared to healthy controls and was associated with increased serum bone-specific alkaline phosphate (BALP) (Fan et al., 2016). In addition to vitamin D deficiency, use of AEDs has been associated with hyponatremia in epilepsy patients. In a cross-sectional study of patients with epilepsy, hyponatremia was observed in ∼10% of the population and was independently associated with decreased BMD and increased risk of osteoporosis, providing evidence that altered sodium metabolism may contribute to AED-associated bone loss in epilepsy (Diemar et al., 2019a). While additional mechanistic studies are needed, current evidence points to altered vitamin D and sodium metabolism, elevated PTH, and dysregulated bone turnover in epilepsy patients taking AEDs.

Neuromuscular Disease

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by loss of cortical, brainstem, and spinal motor neurons that results in progressive muscle atrophy. There is currently no cure for ALS. Most patients eventually become dependent on mechanical ventilation and usually die due to respiratory failure (Portaro et al., 2018). How ALS may affect the skeleton and modify osteoporosis risk is under-studied. Altered calcium metabolism, hypovitaminosis D, reduced cortical bone mass, and vertebral defects have been noted in ALS patients (Mallette et al., 1977; Yanagihara et al., 1984; Joyce et al., 2012). In clinical studies, ALS patients had 14% more fractures than controls, and, in a Swedish population, fracture was associated with higher incidence of ALS (Parfitt, 1994; Peters et al., 2017). ALS has also been associated with increased bone turnover markers in the blood (Fang et al., 2010). In a case report of an 81-year-old man with ALS, multiple hidden vertebral fractures were found, with a low Z score but normal TBS, suggesting normal bone structure (Portaro et al., 2018). It is possible that reduced muscle strength from ALS resulted in an unsupported spinal column, leading to these fractures. In a mouse model of ALS, $SOD1^{G93A}$ mice demonstrated decreased bone mass with notable whole bone biomechanical deficits (Ko et al., 2018). Osteoblasts isolated from $SOD1^{G93A}$ mice with muscle atrophy had impaired differentiation capacity, while osteoclast activity was increased compared to wildtype mice (Zhu et al., 2015). Aberrant Akt, Erk1/2, SOST, RANKL, and β-catenin signaling pathways were noted, which could be further links between ALS-induced muscle atrophy and bone loss. Muscle and bone are known to cross-talk extensively, with skeletal muscle providing an important source of osteogenic growth factors (e.g., IGF-1, FGF-2), as well as driving bone morphogenesis through mechanical load (Hamrick et al., 2010; Sharir et al., 2011; Zhou et al., 2015). Thus, it is likely that muscle atrophy is the key component linking ALS to bone loss and increased fracture risk.

Another interesting mechanism that may link ALS to bone is accumulation of neurotoxic metals. Neurotoxic metals, such

as lead, have been found in the brain and CSF of ALS patients and have been shown to affect bone mineralization, whereby they accumulate in the bone and act as substitutes for calcium in hydroxyapatite (Roos et al., 2013; Chen X. et al., 2014; Roos, 2014). It is also possible that osteoporosis can worsen neurodegenerative disease outcomes, as the bones and CSF share circulation. Bone may act as a sink for neurotoxic metals, releasing them during osteoporosis, thereby facilitating neurodegeneration (Roos, 2014). Patients exposed to high concentrations of neurotoxic metals should be more closely monitored for osteoporosis and frequently tested for neurotoxic metals. It is still unclear how any specific molecular mechanism tied to ALS may influence bone homeostasis or if increased risk is due primarily to lifestyle factors, as age, reduced mobility, increased falls, and weight loss are all prevalent in ALS and are common osteoporosis risk factors. Thus, more studies are needed examining molecular mechanisms linking ALS to bone, particularly any associated with muscle atrophy or neurotoxic metals.

Myasthenia Gravis

Myasthenia gravis (MG) is a neuromuscular disorder that results in weakening of the skeletal muscles. It is frequently a product of autoimmune disease, resulting in attack on nicotinic acetylcholine receptors or on muscle-specific tyrosine kinase (MuSK). The exact cause of this autoimmune reaction is still under investigation. Symptoms include difficulty breathing or swallowing, fatigue, drooping of eyelids, problems walking or lifting objects, trouble talking, and double vision. Regarding impacts on bone, a study found that MG resulted in a 1.96-fold increased risk of developing osteoporosis, likely due to lack of outdoor activity leading to decreased sunlight exposure/vitamin D and physical inactivity (Yeh et al., 2014). However, altered acetylcholine signaling may also play a role, as osteoblasts express acetylcholine receptors and elevated acetylcholine levels induce osteoblast proliferation (En-Nosse et al., 2009; Sato et al., 2010). In addition, MG patients prescribed antidepressants, anxiolytics, or anticonvulsants had increased fracture risk (Pouwels et al., 2013). The mechanism underlying this finding is unknown but may be due to altered neuronal signaling, as use of SSRIs reduces BMD in humans (Ducy and Karsenty, 2010; Haney et al., 2010; Brinton et al., 2019). The use of anticonvulsants increases vitamin D catabolism, leading to increased bone resorption (Kinjo et al., 2005). However, how these mechanisms coincide with MG to increase fracture risk remains unknown.

In addition to the effects of MG itself, corticosteroids, a common treatment for MG, are known to cause bone loss, with long-term corticosteroid use the most common mediator of secondary osteoporosis (Buehring et al., 2013). Corticosteroids have been shown to increase osteoporosis risk in MG (Pascuzzi et al., 1984; Konno et al., 2015; Braz et al., 2017). A case study reported an MG patient with eight spinal compression fractures due to intensive and prolonged prednisone treatment, but DEXA scanning and/or bisphosphonate treatment were not mentioned as being used prophylactically (Raibagkar et al., 2017). This situation may, unfortunately, not be uncommon among neurologists, as there may be a lack of awareness and non-implementation of iatrogenic osteoporosis treatment guidelines, with limited requested DEXA scanning and a lack of understanding in how to interpret T scores leading to over- or under-treatment with bisphosphonates (Lewis and Smith, 2001; Lozsadi et al., 2006; Gallagher and Sturrock, 2007). To demonstrate the benefits of prophylactic osteoporosis treatment, BMD in 36 MG patients who had undergone long-term prednisolone administration with concurrent treatment with elcatonin was measured, and a decrease in BMD was found in 31% of female patients and osteoporosis in 11.5% compared to a presumptive rate of 22.6% in the general population. No osteoporosis was detected in male patients (Wakata et al., 2004). This suggests that prednisolone-treated MG patients have an acceptable bone loss risk when monitored and provided prophylactic osteoporosis treatment. Likewise, MG patients with history of glucocorticoid treatment who were treated with alendronate combined with alfacalcidol showed increased BMD and decreased bone turnover biomarker levels (Lv et al., 2018). Further studies are needed to dissect the mechanistic roles by which MG impacts bone health independent of corticosteroid use.

Neuromuscular Dystrophy

Neuromuscular dystrophy (NMD) is a group of degenerative muscle diseases in which genetic mutations result in loss of muscle mass and progressive weakness. Muscle-bone interactions have been extensively studied, and it is thought that alterations in muscle-derived myokines, bone deformation as a result of muscle weakness, and direct effects of genetic defects on bone cells may negatively impact bone in NMD, as well as low vitamin D, nutritional deficits, immobility, and drug treatments (Kurek et al., 1996; Febbraio and Pedersen, 2002; Veilleux and Rauch, 2017).

Duchenne muscular dystrophy (DMD) is the most common form of NMD and is an X-linked recessive disorder linked to a mutation in the dystrophin gene that is characterized by progressive muscle weakness due to reduction of dystrophin and destabilizing effects on the sarcolemmal membrane, ultimately leading to premature death (Hoffman et al., 1987). There is currently no cure. DMD is the most studied form of NMD in regards to bone health, with reports dating back to 1941 (Maybarduk and Levine, 1941; Joyce et al., 2012). Boys with DMD have abnormalities in bone geometry, presenting with slender long-bone shafts, a likely risk factor for long bone fracture (Veilleux and Rauch, 2017). Up to 90% of patients with DMD have scoliosis, providing strong evidence for the role of dystrophin in regulating bone health and development (Pecak et al., 1980). Decreased BMD, increased fracture rate, and vitamin D deficiency have been reported in DMD (Siegel, 1977; Larson and Henderson, 2000; Vestergaard et al., 2001; McDonald et al., 2002; Bianchi et al., 2003; Hawker et al., 2005; Perera et al., 2016; Joseph et al., 2019). Aparicio et al. found that eight out of ten boys aged 6–11 years with DMD years had osteoporosis in the proximal femur, while the remaining two boys had osteopenia (Aparicio et al., 2002). Bianchi et al. showed that DMD patients had reductions in spine BMD, hypocalciuria, increased bone turnover markers, and low vitamin D levels (Bianchi et al., 2003).

Fall risk is also increased with DMD, thereby further increasing fracture risk (McDonald et al., 2002).

Using the dystrophin-null *mdx* mouse, Rufo et al. found *mdx* mice displayed changes in BMD in a manner similar to that observed in humans. Osteoclasts and IL-6 levels were increased, while RANKL:OPG ratio was altered in favor of increased bone resorption. Human primary osteoblasts incubated with sera from DMD patients showed decreased nodule mineralization, downregulation of *OSX* and *OCN*, and upregulation of *IL6*, *IL11*, *inhibin-βA*, and *TGFβ2*, suggesting DMD can directly impact bone at a cellular and molecular level (Rufo et al., 2011). This study also proposed anti-IL-6 therapy as a possible treatment of bone disease in DMD. In regard to current DMD treatment, increasing routine use of corticosteroids to treat DMD is concerning, due to the known effects of chronic glucocorticoid treatment on bone health (Bell et al., 2017). In DMD, corticosteroid use may be increasing prevalence of vertebral fracture (King et al., 2007; Houde et al., 2008; Annexstad et al., 2019). However, robust evidence that corticosteroid use increases fracture risk in DMD, specifically, is lacking. Teriparatide has also been used with success in DMD, showing improvements in BMD and quality of life with few, if any, side effects (Catalano et al., 2016; Nasomyont et al., 2020). It is clear that routine imaging, particularly of the spine, clinical monitoring, consideration of skeletal delay, possible vitamin D supplementation and/or teriparatide treatment are needed when evaluating bone health and BMD Z-scores in patients with DMD (Ko et al., 2020).

Another form of NMD, spinal muscular atrophy (SMA), an autosomal recessive disorder due to mutations in survival motor neuron 1 and (SMN1/2) that involves selective destruction of anterior horn cells, is associated with fractures at birth and increased rates of fracture throughout life. There are multiple subtypes that present with different degrees of severity. Both long bone and vertebral fractures are relatively common, as well as scoliosis (Vai et al., 2015). Animal studies have shown that the exon 7 splice variant of SMN upregulates osteoclast-stimulating factor, promotes osteoclast formation, and enhances bone resorption (Kurihara et al., 2001; Shanmugarajan et al., 2009). However, more in depth mechanistic studies are needed in humans to determine direct effects of SMA mutations on bone.

Psychological

Major Depressive Disorder

Major Depressive Disorder (MDD) is a highly prevalent, heterogeneous mood disorder characterized by biases in attending to and recalling negative emotional stimuli that align with a negative mood state (Belmaker, 2008). The etiology of MDD is complex and likely involves dysregulation of serotonin and norepinephrine neurotransmission, increased neuroinflammation, and environmental factors (Woelfer et al., 2019). Significant clinical evidence shows MDD is associated with poor bone health, including decreased BMD and increased risk for osteoporosis. Patients with MDD were found to be 1.3 times more likely to develop osteoporosis compared to patients without MDD (Lee et al., 2015). In a population-based cohort study, patients diagnosed with a depressive disorder were found to have higher risk of vertebral fracture compared to healthy patients (Lee et al., 2017). In a meta-analysis, MDD was associated with lower BMD in the lumbar spine, femur, and total hip regions in all age groups compared to healthy controls (Schweiger et al., 2016). Differences in lumbar spine and femur BMD were more prevalent in women, whereas differences in hip BMD were more prevalent in men, suggesting sex-dependent effects of MDD on bone. Clinical studies also point to age-dependent differential effects of MDD on bone. Adolescent boys with MDD had lower hip and femoral neck BMD compared to age-matched controls, whereas no differences in BMD were found in girls with MDD compared to healthy controls (Fazeli et al., 2013).

Although many clinical studies examining the impact of MDD on bone do not stratify based on MDD subtype, different subtypes of MDD may be associated with greater risk for low BMD. In a study of premenopausal woman with melancholic, atypical, or undifferentiated MDD, women with undifferentiated MDD were more likely to exhibit low BMD at the femoral neck compared to healthy control patients. Elevated levels of adrenocorticotropic hormone (ACTH) were observed in women with atypical MDD, while higher levels of leptin were observed in women with melancholic MDD, suggesting differences in the pathophysiology between MDD subtypes may also account for observed differences in bone health (Cizza et al., 2010; Woelfer et al., 2019). Psychological conditions commonly co-occurring with MDD, including anxiety, may also contribute to bone loss. In a study of postmenopausal women, patients with higher anxiety levels exhibited decreased lumbar and femoral neck BMD and increased fracture risk compared to patients with lower anxiety levels (Catalano et al., 2018). A separate study in postmenopausal women showed that anxiety level, as determined by the Hamilton Anxiety Rating Scale (HAMA), was inversely correlated with levels of vitamin D and this association was independent of patient level of depression, suggesting that anxiety independently impacts vitamin D metabolism and this may be one mechanism by which anxiety contributes to bone loss and decreased patient quality of life in the aging population (Martino et al., 2018a,b). As SSRIs are used as a first-line therapy for MDD patients and have negative bone effects, it is difficult to parse out how MDD pathophysiology, versus SSRI treatment, impacts bone health. Recurrent MDD in adult men was associated with decreased forearm and total body BMD compared to men with no history of MDD (Rauma et al., 2015). Further, antidepressant use in this population was associated with lower BMD in lower-weight men only. Interestingly, acute MDD episodes were found to be associated with higher BMD at total hip, pointing to differential effects of acute versus recurrent MDD. In a study of adolescents and young adults who were either unmedicated or within 1 month of starting SSRI treatment, SSRI use was associated with increased lumbar spine areal BMD in females and decreased lumbar spine areal BMD in males, suggesting SSRIs independently impact bone health in a sex-dependent manner in MDD (Calarge et al., 2014). In young to middle-aged patients with an acute episode of depression, SSRI use had no impact on BMD (Malik et al., 2013). However, increased levels of OPG and increased levels of physical activity were observed in

MDD patients, suggesting there may be protective/compensatory mechanisms in acute MDD that temper SSRI-mediated bone effects. In a study examining levels of bone turnover markers in medication-free inpatients with recurrent MDD, patients with MDD exhibited decreased levels of baseline OPG/RANKL and plasma OPN, indicating MDD may modulate bone physiology independent of SSRI use (Kadriu et al., 2018).

Bone loss in MDD patients may also be associated with increased activation of the ACTH and PTH axis, dysregulation of the OPG-RANK-RANKL axis, increased inflammation, and autonomic dysfunction (Rosenblat et al., 2016; Elefteriou, 2018). In postmenopausal women, patients with MDD exhibited decreased BMD and increased levels of PTH and RANKL compared to healthy controls (Atteritano et al., 2013). In premenopausal women, patients with MDD exhibited lower BMD at baseline, as well as increased PTH and ACTH at baseline and 6-month follow-up compared to healthy controls (Cizza et al., 2012). Levels of PTH remained higher in MDD patients at 24 months, suggesting sustained activation of the PTH axis may perpetuate negative bone effects. Calcium and vitamin D levels were also significantly decreased in patients with MDD compared to controls, indicating vitamin deficiency is a contributing factor. Increased prevalence of low BMD at the femoral neck and hip was observed in premenopausal women with MDD compared to controls, with a concomitant increase in circulating proinflammatory cytokines (e.g., IL-1β, IL-2, IL-6, TNF-α) (Eskandari, 2007). Significant increases in plasma IL-6 and changes in its diurnal release were also observed in patients with active MDD and found to correlate with mood ratings, providing additional evidence that inflammation may dually mediate neurocognitive effects and bone effects in MDD (Alesci et al., 2005). Patients with MDD also commonly present with autonomic dysfunction (Kemp et al., 2010; Yang et al., 2011; Brunoni et al., 2013). Studies in preclinical models show that MDD-associated trabecular bone loss is associated with increased levels of bone norepinephrine and can be attenuated by treatment with propranolol, a beta-adrenergic antagonist (Yirmiya et al., 2006). Together, these studies implicate increased sympathetic output as a driver of MDD-associated bone loss, although additional clinical studies will be necessary to determine the mechanisms by which altered sympathetic signaling impacts bone in MDD patients. Further, additional clinical studies that carefully control for concomitant SSRI use, MDD subtype and nature (acute versus recurrent), and comorbid conditions such as anxiety, will better our understanding of MDD-driven bone pathophysiology.

Post-traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is characterized by an abnormal, persistent response to a traumatic event (Seal, 2007; Heron-Delaney et al., 2013). Patients with PTSD exhibit re-experiencing symptoms related to the initial traumatic event, such as flashbacks and nightmares, as well as avoidance, arousal/reactivity, cognitive, and mood symptoms, which can manifest as being easily startled, difficulty sleeping, negative thoughts, and angry outbursts (Qi et al., 2016). While the pathophysiology of PTSD is complex and not fully understood, dysregulations in the HPA axis and glucocorticoid signaling, as well as increased neural and systemic inflammation, have been implicated in disease initiation and development (Girgenti et al., 2017; Dunlop and Wong, 2019).

In addition to primary psychological symptoms, studies in adult, elderly adult, Veteran, and Prisoner of War populations provide substantial evidence that PTSD negatively impacts bone health (Glaesmer et al., 2011; Hain et al., 2011; Huang et al., 2018). A large nationwide longitudinal study showed adults with PTSD were more likely to develop osteoporosis at an earlier age, compared to age-matched, healthy controls (Huang et al., 2018). Similarly, the National Health and Resilience in Veterans study showed that U.S. Veterans diagnosed with PTSD had significantly increased risk for developing osteoporosis or osteopenia (El-Gabalawy et al., 2018). Evidence also supports that PTSD patients have an increased fracture risk (Jiang et al., 2018).

While the mechanisms by which PTSD impacts bone health have not been fully elucidated, several molecular, hormonal, and immune-related pathways implicated in PTSD pathophysiology negatively impact bone and have been extensively reviewed elsewhere (Kelly et al., 2019). In response to a stressor, stimulation of the glucocorticoid axis can lead to activation of inflammatory and RANK pathways via NF-kB, decreased osteoblast function, and prolonged osteoclast viability (Vega et al., 2007; Briot and Roux, 2015). Stress-induced increases in catecholamines, the "fight-or-flight" hormones, can also lead to activation of β-adrenergic receptors, stimulating RANKL expression and promoting osteoclast differentiation (Rodrigues et al., 2012). In a mouse model of PTSD, PTSD was associated with significantly decreased BMC and BMD in the femur, lumbar vertebra, and tibia 3 weeks following initial trauma, providing evidence that activation of the stress response in PTSD mice leads to bone loss (Yu et al., 2012). In addition to dysregulated glucocorticoid and stress hormone signaling, changes in IGF signaling and immune activation may contribute to PTSD-related bone loss. IGFs have been implicated in stress signaling and are known to be important regulators of the osteoblast-osteoclast balance (Canalis, 2009; Zegarra-Valdivia, 2017). IGF-1 supports osteoblast differentiation, with decreasing levels of IGF-1 in the aging population being associated with osteoporosis (Perrini et al., 2010; Crane et al., 2013). Increased levels of inflammatory factors, including IL-1β, IL-6, and TNF-α, are upregulated in patients with PTSD and have been implicated in mediating neurocognitive effects of the disorder (Passos et al., 2015; Lindqvist et al., 2017; Imai et al., 2018). Proinflammatory cytokines also promote osteoclast formation and amplify bone resorption (Sims, 2016; Weitzmann, 2017). These studies suggest PTSD-induced inflammation may negatively impact bone health, although additional studies are needed to delineate these effects.

In addition to shared mechanisms of pathophysiology, therapies used to treat PTSD may also negatively impact bone health. First- and second-line treatment options for PTSD patients, including SSRIs and antipsychotic drugs, are associated with increased risk of developing osteoporosis and fracture (Vestergaard et al., 2006, 2008; Haney et al., 2010; Alexander, 2012; Rabenda et al., 2013; Seifert and Wiltrout, 2013; Rauma

et al., 2015). Therefore, it is reasonable to speculate that SSRI use may exacerbate PTSD-associated bone loss. However, clinical evidence of the combined effects of PTSD and SSRI use on bone health is currently lacking.

Substance Abuse and Addiction

Substance use disorders (SUDs), including addictions to alcohol, heroin, cannabis, ecstasy, cocaine, and amphetamines, are a major global health concern. While addiction to different substances can produce different neurobiological effects, there are shared layers of symptomology between different substance groups. These include a reduction in response to normal biological activities like social cooperation and a loss of ability to control drug-seeking behavior. Progressive changes in dopamine transmission in the corticolimbic brain regions, alterations in glutamatergic synapses, and environmental stress have been implicated in the initiation and development of SUDs (Reid et al., 2012).

In addition to changes in neural circuitry and plasticity, SUDs have been associated with impaired bone health. The impact of alcohol addiction on bone has been well studied and will be the focus of this section, although opioid, cannabis, and amphetamine addictions have also been associated with decreased BMD and increased fracture risk (Gozashti et al., 2011; Mosti et al., 2016; Gotthardt et al., 2017; Heydari et al., 2017; Sophocleous et al., 2017). Chronic-excessive use of alcohol has been shown to negatively impact bone health, resulting in decreased BMD, decreased BMC, and increased fracture risk. In a study of males classified as heavy drinkers, osteopenia was observed in 23% of the population, with a significant inverse correlation observed between total alcohol intake and BMD (González-Calvin et al., 2009). In another study of chronic alcoholic males, 34% of patients had osteoporosis, with low BMD in the femoral neck and lumbar spine compared to age-matched, healthy controls (Peris et al., 1995). In addition to increased risk of vertebral and non-vertebral fractures, chronic male alcoholics exhibited increased ALP and BALP, as well as significantly reduced vitamin D and BGP levels (Santori et al., 2008). Together, these studies point to impaired bone formation as the major mechanism by which alcohol addiction impacts bone. Although less well studied, chronic female alcohol users also exhibit impaired bone health. In a cross-sectional study of women aged 18–70 years, chronic alcohol users exhibited decreased femoral neck and lumbar spine BMD and had a higher prevalence of fractures compared to non-alcohol-abusing women, although fracture risk could not be attributed to alcohol use alone (Clark et al., 2003). In a study of both male and female chronic alcohol users, BMD directly correlated with total cholesterol and LDL-cholesterol, independent of liver function, providing evidence that alcohol addiction may mediate changes in lipid profiles that have separate effects on bone health. Together, these studies provide evidence that alcohol abuse negatively impacts bone health and is closely intertwined with sex, overall nutrition, and vitamin D deficiency.

Due to the nature of SUDs, it is difficult to parse out the effects of substance versus substance-induced neurological changes on bone. *In vitro* studies provide evidence that alcohol can directly impact the osteoblast:osteoclast balance. Treatment of BM cultures with alcohol or acetaldehyde directly impaired osteoblast differentiation, decreased osteogenesis, and promoted adipogenesis (Giuliani et al., 1999; Cui et al., 2011). Further, ethanol treatment increased bone resorption by osteoclasts *in vitro* (Cheung et al., 1995). In a rabbit model of alcoholism, increased triglyceride-bearing osteocytes and increased empty lacunae were observed, suggesting alcohol leads to impaired osteocyte function and may promote osteocyte apoptosis (Wang et al., 2003). Preclinical studies also point to a role for alcohol-induced changes in leptin signaling, resulting in impaired osteogenesis and increased adipogenesis (Wang et al., 2003; Otaka et al., 2007; Maurel et al., 2011). In alcoholism and other SUDs, it is likely that both direct effects of the substance itself and indirect effects (e.g., neurobiological impacts on bone turnover) are responsible for impaired bone health and will require further study to fully dissect.

Trauma and Spinal Cord

Acute Spinal Cord Injury

The global incidence of spinal cord injury (SCI) is 10.4–83 cases/million/year. Bone loss below the level of the lesion is rapid and as high as 4% per month in trabecular bone and 2% per month in cortical bone (Wilmet et al., 1995; Szollar et al., 1997; Dauty et al., 2000). This bone loss persists for ∼2 years post-SCI, with peak loss at 3–5 months, resulting in increased risk of fracture and osteoporosis (Roberts et al., 1998; Maïmoun et al., 2006; Smith and Carroll, 2011). Post-SCI, bone resorption markers increase with a lack of concomitant increase in bone formation markers (Smith and Carroll, 2011; Thakkar et al., 2020). Numerous mechanisms have been implicated in SCI-related bone loss, including mechanical unloading from loss of motor function, as well as metabolic, endocrine, neural denervation, and vascular changes (Jiang et al., 2006b). Each of these can result in osteoblast:osteoclast imbalance, leading to bone loss, osteoporosis, and fragility fractures. In the absence of mechanical strain, osteocytes signal to reduce osteoblast activity, resulting in reduced bone formation (Jiang et al., 2006a,b). SCI also impacts the OPG-RANKL system and Wnt signaling, shifting the balance to bone resorption over bone formation (Maïmoun et al., 2006; Bonewald and Johnson, 2008). Altered vasoregulation due to injury impacts viability of oxygen and nutrients to bone, promoting osteoclast formation and bone resorption (Jiang et al., 2006a,b). Decreased innervation due to SCI may also affect availability of neuropeptides, such as vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP), which suppress bone resorptive activities through RANKL/OPG pathway (Yoon et al., 2004). Decreased PTH has also been reported 4–12 months post-SCI, which can lead to decreased vitamin D and subsequent impaired absorption of dietary calcium (Giangregorio and Blimkie, 2002; Jiang et al., 2006a,b). Thus, while disuse is considered to be the most impactful factor in post-SCI osteoporosis and associated fractures, it is clearly a more complex, multi-factorial process, and this should be considered when developing therapeutic strategies.

Traumatic Brain Injury

Traumatic brain injury (TBI) results in temporary to permanent neurological damage and dysfunction and is associated with increased mortality and morbidity. TBI is often referred to as the "silent epidemic," and, while the incidence has been difficult to determine, reports suggest 69 million individuals suffer TBI from all causes annually (Dewan et al., 2019). Patients with TBI exhibit an elevated risk for fracture and reduced BMD. A recent study demonstrated that patients recovering from TBI had suboptimal BMD measurements that were low for their age and gender, with 18% of the participants meeting criteria for osteopenia measured at the radius and 51% meeting the criteria for osteopenia/osteoporosis measured at the tibia (Banham-Hall et al., 2013). Markers of bone turnover, including OCN, type I collagen, and PTH, were dysregulated during the early post-traumatic period, suggesting an imbalance between bone formation and resorption that occurred rapidly post-injury (Trentz et al., 2005). Recent preclinical studies suggest inflammatory stress on bone and BM following TBI leads to NFκB activation, which, in turn, induces osteoclastogenesis and bone resorption (Singleton et al., 2019). Pre-clinical studies from Mohan's group using a repetitive mouse TBI model have shown reduced BMC, bone area, bone strength, and BMD in TBI mice accompanied by negative impacts on cortical structure and trabecular architecture (Yu et al., 2014a,b). Their work also demonstrated that mild TBI and bony effects were associated with decreased circulating IGF-1 levels (Yu et al., 2014a). Pituitary dysfunctions post-TBI are common, present in 25–70% of patients (Rosario et al., 2013). Deficiencies in pituitary hormones, including those that impact bone formation and contribute to peak bone mass (e.g., IGF-1), can result in negative effects on skeletal maintenance (Mohan et al., 2003; Mohan and Baylink, 2005; Xing et al., 2012). An additional contributor to low BMD risk in TBI patients is the use of anti-epileptic drugs, which induce the cytochrome P450 system and likely increase the conversion of vitamin D to its inactive forms, resulting in less biologically active vitamin D, decreased calcium absorption, hypocalcemia, increased PTH levels, and compensatory mobilization of calcium stores from bone (Smith et al., 2016). Polytrauma with TBI and concomitant fracture has been shown to result in higher functional deficits and mortality rates (Albrecht et al., 2019). Studies using two mouse models of TBI showed that neurological inflammation and brain damage was increased in animals with fracture and that this damage could be alleviated by blocking the inflammatory effects of fracture (Shultz et al., 2015; Yang et al., 2016). While mechanisms driving the effects of fracture on TBI outcomes are still being elucidated, these studies suggest that exacerbated neuroinflammation may be an important contributing factor.

Vascular Disease

Stroke

Stroke is one of the most common neurologic problems, with hemiplegia being a common outcome that results in loss of voluntary movement, immobilization, and sensory disturbances. There is a robust and long literature examining the effects of stroke on bone health and fracture, notably in the hip (Peszczynski, 1957). The relative risk of fracture after hospitalization for stroke is greater than 7 times the rate of fracture in age- and sex-matched control populations (Kanis et al., 2001). BMD is lower following stroke, while low BMD may also be a prospective risk factor for stroke (Ramnemark et al., 1999; Jørgensen et al., 2000; Myint et al., 2007, 2014; Lee et al., 2013; Lam et al., 2016). Low BMD may increase stroke risk through altered estrogen/OPG signaling that leads to increased risk of intracerebral hemorrhage (Strand et al., 2007). Cibelli et al. showed that aseptic long bone fracture caused neuroinflammation and cognitive decline (Cibelli et al., 2010). Thus, determining the cause-and-effect relationship between stroke and fracture can be complex. A meta-analysis showed that, in subacute and chronic stroke, skeletal sites in the affected/paretic limbs had greater decline in bone quality and deleterious changes in bone geometry compared to unaffected/non-paretic limbs. This rate of change slowed as post-stroke duration increased, with the greatest changes occurring in the first few months post-stroke. A strong relationship between bone density/strength index and muscle strength/mass was also noted, demonstrating the importance of muscle-bone interactions and how they may act as a functional unit, as proposed by Schoenau (2005). These findings suggest muscle strength training and early intervention are key to minimizing negative bone effects of stroke (Borschmann et al., 2018; Yang et al., 2020). To this end, a mix of resistance, aerobic, and dynamic loading exercises resulted in better bone outcomes in the hip and tibia on the affected side in chronic stroke patients (Pang et al., 2005, 2006).

Muscle imbalance may not be the only mechanism by which stroke affects bone health. Lower bone turnover markers have been noted in serum from stroke patients, suggesting dysregulated remodeling at the bone multicellular unit (Sato et al., 2000). Stroke patients also have higher energy expenditure, with this interruption of energy homeostasis potentially negatively impacting the skeleton during bone remodeling (Detrembleur et al., 2003; Lee et al., 2007; Driessler and Baldock, 2010). Additionally, reduced vitamin D levels, degree of recovery, increased fall risk, and use of anticoagulants may increase bone loss post-stroke (Jørgensen et al., 2000; Smith and Carroll, 2011; Batchelor et al., 2012; Signorelli et al., 2019). Thus, increased bone screening measures are needed in stroke patients, as screening may currently be infrequent (Kapoor et al., 2019). Osteoporosis treatments, such as bisphosphonates, may be beneficial for preserving BMD post-stroke, but there is little evidence to date (Hsieh et al., 2020). More studies are needed to dissect the molecular mechanisms at the intersection of bone and stroke to guide treatment and screening recommendations.

Other Disorders

Chronic Fatigue

Chronic fatigue syndrome (CFS) is a complex neurological disorder associated with persistent, overwhelming fatigue that affects > 3% of the population in Western countries and is more prevalent in women (Griffith and Zarrouf, 2008). Diagnostic

criteria include severe, persistent fatigue for at least 6 months, exclusion of other medical disorders, and observation of at least four minor symptoms, including impaired memory, nausea, extreme post-exertion fatigue, headaches, muscle pain, sore throat, and poor sleep (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome et al., 2015). There remains a lack of treatment and diagnostics tools for CFS, although glucocorticoids have been used (McKenzie et al., 2000). Bone loss and increased fracture risk have been reported in individuals with CFS, independent of glucocorticoid use. Hoskin et al. found that hip BMD was approximately 7% lower in women with CFS (Hoskin et al., 2006). A prospective study reported a 1.16-fold increased risk of fracture in the CFS cohort without osteoporosis compared to the non-CFS cohort (Chen C.-S. et al., 2014). However, no mechanistic insights were provided in these studies. Other studies have reported that IGF-1 levels are altered in CFS patients (Buchwald et al., 1996; Berwaerts et al., 1998; Cleare et al., 2000; Nijs et al., 2003). IGF-1 is essential for osteoblast proliferation, thus impaired secretion could lead to bone loss. Studies are needed to further characterize those CFS patients with low serum IGF-1 to determine if these subgroups have increased fracture risk compared to CFS patients with normal or high levels of IGF-1. High prevalence of mycoplasma infections has also been reported in CFS patients (Choppa et al., 1998; Nasralla et al., 1999), which can stimulate macrophage activation and release of pro-inflammatory cytokines that enhance osteoclast activity. *M. fermentans* has been shown to produce 2-kDa macrophage-activating lipopeptide (MALP-2), which stimulates macrophages and bone resorption in a dose-dependent manner and is increased with CFS (Piec et al., 1999). Thus, chronic fatigue may induce bone loss or increase fracture risk through increased inflammation and/or dysregulation of growth factors.

Sleep Disorders

Chronic sleep deprivation is becoming a widespread problem, with at least one-third of adults reporting less than 6.5 h of sleep per night compared to about 9 h of average sleep in the early 1900s (Bonnet and Arand, 1995; Spiegel et al., 1999; Specker et al., 2007). Sleep deprivation can negatively impact health by decreasing cardiovascular health and increasing risk for development of diabetes and obesity. Since circadian rhythm has been extensively shown to regulate bone, sleep disorders may also affect bone homeostasis (Swanson et al., 2015, 2018; Song et al., 2018). Spiegel et al. found that cortisol concentrations were higher in the evening with sleep deprivation, a known risk factor for bone loss (Spiegel et al., 1999). Three weeks of sleep restriction has been shown to cause a decline in N-terminal propeptide of type 1 procollagen (P1NP), a bone formation marker, with stable resorption markers (e.g., CTX), suggesting an uncoupling of bone remodeling. Importantly, this observed decrease in P1NP was not rescued with ongoing exposure, suggesting BMD could be lowered over time when paired with poor sleeping habits (Swanson et al., 2017, 2019). Sleep-deprived women had lower cortical BMD compared to women with normal sleeping habits, and sleep quality, sleep latency, and sleep timing, but not sleep duration, were associated with osteopenia and sarcopenia in middle-aged individuals (Specker et al., 2007; Lucassen et al., 2017). Shiftwork may also lower BMD, providing evidence that circadian rhythm, and not just amount of sleep, can significantly impact bone (Quevedo and Zuniga, 2010; Kim et al., 2013).

Obstructive sleep apnea (OSAS) has also been shown to lower BMD and vitamin D levels, possibly due to increased hypoxia, which can cause oxidative stress, SNS activity, endothelial dysfunction, and stimulation of osteoclasts (Shahar et al., 2001; Arnett, 2010; Uzkeser et al., 2013; Terzi and Yılmaz, 2016; Eimar et al., 2017). Further, OSAS increases systemic inflammation, with resultant increased IL-6, TNF-α, and C-reactive protein (CRP) production, known risk factors for bone loss (Tomiyama et al., 2008). Fracture can also affect sleep disturbance, likely due to effects on emotional well-being (Shulman et al., 2015). Likewise, vertebral fractures have been associated with poor sleep, and those with osteoporosis were 67% more likely to report decreased sleep. These studies suggest a negative feedback loop may be occurring between reduced sleep and poor bone health (Silverman, 1992; Foley et al., 2004). Interestingly, Cikrikcioglu et al. found that women with restless legs syndrome had increased lumbar BMD, despite lower vitamin D levels, possibly due to unconsciously performing exercise (Cikrikcioglu et al., 2016).

Thus, there are many mechanisms that may link disrupted sleep to bone loss, including increased systemic inflammation, hypoxia, insulin resistance, and oxidative stress, as well as altered circadian rhythm, decreased growth hormone secretion, and physical inactivity. Large-scale, prospective studies are needed to elucidate if sleep loss and/or OSAS are independent risk factors for osteoporosis (Schiza et al., 2013). Further, other sleep disorders, such as narcolepsy or somnambulism, need to be studied in more detail for their potential effects on bone.

Vertigo

Vertigo is a symptom in which someone feels like they are moving or surrounded by moving objects when they are not. This can be associated with nausea, sweating, vomiting, hearing loss, and/or difficulties in walking and balance. As bone mediates hearing and movement and vestibular changes alter SNS output, vertigo may be linked to alterations in bone (Radaei and Gharibzadeh, 2013; Mendy et al., 2014; Yates et al., 2014). Although there are many types of vertigo, one of the most common types, benign paroxysmal positional vertigo (BPPV), has been studied in the context of BMD and vitamin D changes. BPPV is a vestibular dysfunction that is typically unilateral and characterized by short, intense episodes of vertigo. BPPV represents 20–30% of dizziness diagnoses, with no current consensus on its etiology and pathogenesis (Grill et al., 2014; Bazoni et al., 2020). However, the incidence of BPPV increases with age and is believed to involve abnormal stimulation of the cupula by otoliths in any of the three semicircular canals upon changes in head position (Furman and Cass, 1999).

Some studies have noted that reductions in bone mass correlate with both occurrence and recurrence of BPPV (Vibert et al., 2003; Jang and Kang, 2009; Jeong et al., 2009; Kim et al., 2017; Wu et al., 2018; Wang et al., 2020). A meta-analysis found significantly higher incidence of osteoporosis and osteopenia in BPPV patients (He et al., 2019). In addition, BPPV has been

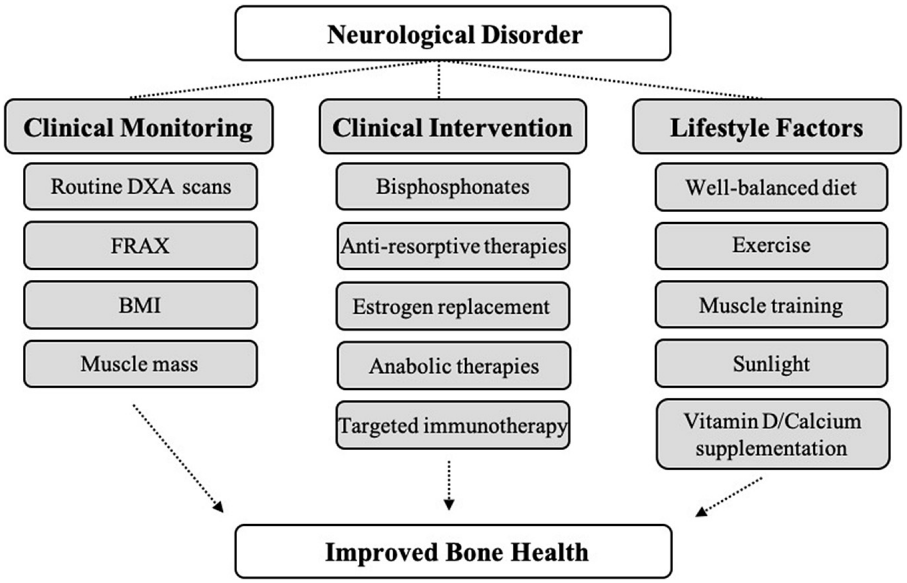

FIGURE 1 | Proposed methods to improve bone health in patients with neurological disorders. There is considerable clinical evidence demonstrating negative impacts of neurological diseases on bone across many disease categories. Patients with neurological diseases exhibit decreased BMD, as well as increased risk for osteoporosis and fracture. Careful clinical monitoring, clinical intervention, and positive lifestyle changes may lead to better bone outcomes in certain subsets of neurological disease patients.

associated with vitamin D deficiency, which can affect both bone and the inner ear (Jeong et al., 2013). BPPV frequently occurs in females over 50 years old, suggesting estrogen loss may be involved in onset (Vibert et al., 2003). Incidence of BPPV recurrence was significantly higher in post-menopausal women with osteoporosis (56.3%) than those with normal BMD (16.1%), and frequency of recurrence increased with decreasing BMD (Yamanaka et al., 2013). Estrogen deficiency can cause low bone mass by altering calcium metabolism, inducing a calcium insufficiency (Riggs et al., 1998). Calcium is important in the synthesis and absorption of otoconia and otoliths, which mature by absorbing calcium. Thus, if there is a shortage of calcium with reduced bone mass, incomplete maturation of otoliths could occur, leading to BPPV. The otolith also acts as a calcium reservoir to maintain calcium homeostasis when necessary, such as in postmenopausal women with osteoporosis (Campos et al., 1999). Thus, altered calcium metabolism caused by decreased estrogen secretion may be a pathophysiological mechanism shared by both BPPV and osteoporosis. Additionally, as electrical signals from the inner ear are relayed to the CNS to maintain body balance and vestibular dysfunction alters SNS output, vertigo may affect bone remodeling and bone mass, as well as fall risk, leading to increased fracture risk. In support of this, fracture risk has been shown to be increased with BPPV (Nakada et al., 2018). Likewise, the reduction in bone mass caused by vertigo may further alter calcium metabolism, increasing vertigo incidence and creating a negative feedback loop. Osteoporosis is, therefore, a risk factor for BPPV recurrence and prognosis may be clinically predicted by BMD reduction, while BPPV itself may increase osteoporosis-related fracture incidence.

CONCLUSION

It is becomingly increasingly clear that bone is a dynamic organ with complex signaling responses throughout the body. Recent studies have led to a better understanding of the brain-bone axis, which regulates skeletal metabolism, hormonal response, and sensory innervation. In this review, we discussed how different neurological disorders impact bone health and how bone itself can affect cognitive function and development. Across many subcategories of neurological disease, there is direct pre-clinical and clinical evidence that deficits in the brain can cause deficits in the bone, including osteopenia/osteoporosis and increased fracture risk. This is due to a complex mixture of neuronal (e.g., SNS/PNS dysregulation), psychological (e.g., HPA/stress), mechanical (e.g., muscle-bone interactions), cellular (e.g., macrophage, neuron, osteoblast, osteoclast), molecular (e.g., IGF-1, IL-6, PTH, Wnt), lifestyle (e.g., falls, malnutrition, physical inactivity, vitamin D deficiency), and treatment (e.g., AED, glucocorticoid, SSRI) factors. Current treatments for osteoporosis, including bisphosphonates, estrogen replacement therapy, and anabolic therapies (e.g., teriparatide, romosozumab) may be beneficial for certain subsets of patients with neurological diseases (**Figure 1**). A better understanding of the mechanisms that lead to bone loss in neurological disorders is of clinical importance and may better inform treatment approaches, encourage lifestyle change, and aid in development of novel osteoporosis therapies. Similarly, a better understanding of how bone regulates the brain will provide new insights into the etiology and development of neurological disorders. Clinicians should consider taking a whole-body approach when treating neurological patients and ensure that treatments directed at the

brain (e.g., glucocorticoids) are not causing deleterious effects elsewhere in the body, such as in the skeleton, which may concurrently signal through negative feedback loops to impact disease severity.

NOMENCLATURE

Aβ, Amyloid-β; ACTH, Adrenocorticotropic Hormone; AD, Alzheimer's Disease; AED, Anti-Epileptic Drug; AKT, Protein Kinase B; ALP, Alkaline Phosphatase; ALS, Amyotrophic Lateral Sclerosis; ApoE, Apolipoprotein E; App, Amyloid Precursor Protein; APT, Antipsychotic Therapy; ASD, Autism Spectrum Disorder; BALP, Bone-Specific Alkaline Phosphatase; BBB, Blood-Brain Barrier; BGP, Bone GLA Protein; BM, Bone Marrow; BMC, Bone Mineral Content; BMD, Bone Mineral Density; CBZ, Carbamazepine; CFS, Chronic Fatigue Syndrome; CGRP, Calcitonin Gene-Related Peptide; CNS, Central Nervous System; CP, Cerebral Palsy; CRP, C-Reactive Protein; CSF, Cerebrospinal Fluid; CTX, C-Terminal Telopeptide Of Type I Collagen; DEXA, Dual-Energy X-Ray Absorptiometry; DMD, Duchenne Muscular Dystrophy; DRN, Dorsal Raphe Nucleus; EBV, Epstein-Barr Virus; EDSS, Expanded Disability Status Scale; EIAED, Enzyme-Inducing Anti-Epileptic Drug; ERK, Extracellular Signal-Regulated Kinase; FDRA, Friedreich Ataxia; FRAX, Fracture Risk Assessment; GMFCS, Gross Motor Function Classification System; GPR158, G Protein-Coupled Receptor 158; HAMA, Hamilton Anxiety Rating Scale; HPA, Hypothalamic-Pituitary-Adrenal; IκB-α, Nuclear Factor Of Kappa Light Polypeptide Gene Enhancer In B-Cells Inhibitor, Alpha; IGF-1, Insulin-Like Growth Factor-1; IL, Interleukin; LDL, Low-Density Lipoprotein; LRP5/6, Lipoprotein-Receptor-Related Protein-5/6; MALP-2, 2-kDa Macrophage-Activating Protein; mBMD, Metacarpal Bone Mineral Density; MCI, Mild Cognitive Impairment; MDD, Major Depressive Disorder; MG, Myasthenia Gravis; MJD, Machado-Joseph Disease; MS, Multiple Sclerosis; MuSK, Muscle-Specific Tyrosine Kinase; NEIAED, Non-Enzyme-Inducing Antiepileptic Drug; NF-κB, Nuclear Factor Kappa B; NFT, Neurofibrillary Tangle; NMD, Neuromuscular Dystrophy; OCN, Osteocalcin; OPG, Osteoprotegerin; OPN, Osteopontin; OSAS, Obstructive Sleep Apnea; OSX, Osterix; P1NP, N-Terminal Propeptide Of Type I Collagen; PD, Parkinson's Disease; PNS, Parasympathetic Nervous System; PTH, Parathyroid Hormone; PTSD, Post-Traumatic Stress Disorder; RANK, Receptor Activator of Nuclear Factor Kappa B; RANKL, Receptor Activator of Nuclear Factor Kappa B Ligand; SAD, Substance Use Disorder; SAE, Sepsis-Associated Encephalopathy; SCI, Spinal Cord Injury; SMA, Spinal Muscular Atrophy; SMN, Survival Motor Neuron; SNS, Sympathetic Nervous System; SOST, Sclerostin; SSRI, Selective Serotonin Reuptake Inhibitor; SUD, Substance Use Disorder; TBI, Traumatic Brain Injury; TBS, Trabecular Bone Score; TGF-β2, Transforming Growth Factor Beta 2; TNF-α, Tumor Necrosis Factor Alpha; TREM2, Triggering Receptor Expressed On Myeloid Cells-2; VIP, Vasoactive Intestinal Peptide; Wnt, Wingless-Type Murine-Mammary-Tumor Virus Integration Site.

AUTHOR CONTRIBUTIONS

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

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Clinical Psychological Figures in Healthcare Professionals: Resilience and Maladjustment as the "Cost of Care"

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Background: The health professionals are involved in the paths of care for patients with different medical conditions. Their life is frequently characterized by psychopathological outcomes so that it is possible to identify consistent burdens. Besides the possibility to develop pathological outcomes, some protective factors such as resilience play a fundamental role in facilitating the adaptation process and the management of maladaptive patterns. Personal characteristics and specific indexes such as burdens and resilience are essential variables useful to study in-depth ongoing conditions and possible interventions. The study was aimed at highlighting the presence and the relations among factors as personal variables, burdens, and resilience, to understand health professionals' specific structure and functions.

Methods: The observation group was composed of 210 participants, 55 males (26.2%), and 155 females (73.8%), aged from 18 to 30 years old with a mean age of 25.92 years old ($SD = 3.33$). The study considered personal characteristics of the subjects, such as age, gender, years of study, days of work per week, hours of work per week, and years of work. Our study had been conducted with the use of measures related to burdens (Caregivers Burden Inventory) and resilience (Resilience Scale for Adults).

Results: The performed analyses consisted of descriptive statistics, correlations, and regressions among the considered variables. Several significant correlations emerged among personal characteristics, CBI, and RSA variables. Specifically, age and work commitment indexes appeared to be significantly related to the development of burdens, differently from the years of study. Significant correlations emerged among personal and RSA variables, indicating precise directions for both domains. Age and gender were identified as predictors to perform multivariate regression analyses concerning CBI factors. Significant dependence relations emerged with reference to all CBI variables.

Conclusion: Pathological outcomes and resilience factors represent two sides of the health professionals' experiences, also known as "invisible patients." Greater knowledge

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about present conditions and future possibilities is a well-known need in literature so that the current analyses considered fundamental factors. In line with state of the art, future studies are needed in order to deepen elusive phenomena underlying maladjustment.

Keywords: healthcare professionals, caregivers, burden, clinical psychology, resilience (psychological)

INTRODUCTION

The healthcare professions expose the subjects to different pathological dynamics, which may retroactively refer to them depending on working conditions and clinical issues. In general, many contributions in literature highlighted how the health status of caregivers meets different challenges, of physical, mental, and management order, extended to their personal life up to the threshold of mortality (Schulz and Beach, 1999; Von Känel et al., 2003; Aschbacher et al., 2006; Kannan et al., 2011; Iavarone et al., 2014). The personal characteristics of these "invisible patients" (Bevans and Sternberg, 2012; Adelman et al., 2014) represent relevant variables since the burdens they have to bear are always relative to the intersection of personal and professional life.

The risks are well-known and well-presented in the literature; for 30 years, many classic studies considered the main variables of the subjects assisting patients with heterogeneous pathological conditions and adverse experiences (Provencher, 1996; Greenberg et al., 1997; Shdaifat and Manaf, 2012; Nikmanesh and Shahinfar, 2016; Di Giuseppe et al., 2018, Di Giuseppe et al., 2019b; Guicciardi et al., 2019; Marchi et al., 2019). In a previous article, it was highlighted how health professionals could meet diametrically opposed dynamics presenting strengths and significant vulnerabilities (Settineri et al., 2019a, Settineri et al., 2019c). The relationships emerged among variables such as well-being, compassion, burnout, and emotional state, pointed out the possible adverse outcomes that caregivers face.

Specifically, constant contact with pathological realities can produce maladjustment from both a professional and health point of view. Dysphoric polarities and low levels of well-being emerged as dominant traits, along with dynamics of compassion and strengths.

What dominates the literature on the caregivers' theme is the need to implement the knowledge about the phenomena and the solution of the pathological outcomes of caregivers.

Similarly, Merlo et al. (2020a) highlighted two precise faces about the profession of caregiver, respectively, referring to compassion and suppression of disturbing contents that tend to be transported into their private life. The impact of these operations on the community is fundamental. Still, it cannot be too far from the personal dynamics of the caregivers who always have to solve the existing ambivalence between compassion satisfaction and fatigue (Hadjistavropoulos et al., 1994; Hundall Stamm, 2009; Collins and Swartz, 2011; Makic, 2015; Velutti et al., 2017; Lynch et al., 2018; Wood et al., 2018; Settineri et al., 2019f; Allday et al., 2020).

A large amount of scientific contributions has dealt with caregivers in general terms. A particular category of caregivers in terms of age is that of the subjects at the beginning of their career. Despite the prevalence of health professionals who practice this profession who are of adulthood, there are many cases in which young professional caregivers could immediately begin to experience the pathological conditions of the patients (Hawken et al., 2019).

In particular, the dynamics taken into consideration in this study referred to specific possibilities and outcomes. First of all, the issue is relating to the various types of caregivers' burden.

Previous articles considered the concept of the burden since caregivers presented a decreased quality of life and specific relationships to the pathological conditions of the assisted subjects (Shdaifat and Manaf, 2012; Grant et al., 2013; Nikmanesh and Shahinfar, 2016; Widowati et al., 2018). The concept of burden clearly represents a homogeneous set of phenomena present in the entire population, as stated by Chou (2000) in his conceptual analysis of the involved dynamics.

As reported by Liang et al. (2018), several studies highlighted predictors and risk factors of this profession, including female gender (Gallicchio et al., 2002), low education (Gallagher et al., 1989; Vincent et al., 2009; Wong et al., 2012; Adelman et al., 2014; Cole et al., 2014), sleep deprivation, economic distress, mood disorders, isolation, and different material restrictions.

Among the possible experiences, the high probability of developing adverse outcomes in psychopathological terms is well-known. This is not the only choice, since we are witnessing the presence of adaptation conditions that respond to the logic of compassion satisfaction. Compassion satisfaction represents a protective factor with respect to the negative possibilities hitherto treated. Specifically, some contributions in literature allowed us to evaluate its role together with work activities (Stamm, 2002; Hundall Stamm, 2009; Collins and Swartz, 2011; Makic, 2015; Lynch et al., 2018; Allday et al., 2020).

In general, this ambivalence testifies to the fact that caregivers and healthcare professionals must be in a position of resistance to those phenomena bringing them closer to negative outcomes. The concept of resilience first appeared in 1992 (Werner and Smith, 1992; Peveri, 2009) as the first example of a clear conceptualization of the phenomenon.

The origin of the term is of a different domain since, in physics, it represents the attitude of a body to resist without breakage following abrupt or lasting external mechanical stresses (Devoto, 1971).

The conceptualization they introduced into the domain of the psychological disciplines has dealt with the neuroscientific and psychobiological side, with particular reference to traumatic experiences (Edelman, 1992; Damasio, 1994; Le Doux, 1996; Cyrulnik and Malaguti, 2005; Malaguti, 2005; Putton and Fortugno, 2006; Motofei and Rowland, 2015, 2016, 2018).

Resilience, based on various contributions in the literature (Rutter, 1987, Rutter, 1990, Flach, 1988; Fine, 1991; Garmezy,

1993; Rutter, 2007), represents a dynamic phenomenon, which, depending on the environmental conditions, leads the subject to get closer to adaptation.

An integrative contribution (Richardson, 2002) brought together the existing approaches, essentially distinguishing two research phases and coming to the conclusion that resilience factors are present since birth and can be differently enhanced during the life span (Peveri, 2009).

Recent research papers (Harmell et al., 2011; Fernández-Lansac et al., 2012; Lin et al., 2013; Dias et al., 2015) continue to confirm the centrality of resilience with respect to the adaptation possibilities of caregivers. Among these, a review according to the conceptual aspects of the term resilience highlighted that various factors contribute to the caregivers' well-being (Lin et al., 2013).

Factors such as disposition patterns, situational patterns, relational patterns, and cultural patterns represented the dimensional constructs of resilience for caregivers working with children experiencing the chronic condition. Harmell et al. (2011) reported the higher levels of personal mastery and self-efficacy of caregivers as the main finding, showing their capacities in the light of protective issues.

According to Chapman et al. (2020), some fundamental frameworks need to be considered about resilience. Some contributions treated by the authors exemplified this need as pointed out through the interest for the adverse events (Bonanno, 2004) and the related maladaptive outcomes (McVicar, 2003).

With particular reference to Wright et al. (2013), the authors reported the definition of an adverse event as: *"disturbances to the function or viability of a system"* (p. 17). It is clear that the theme of adversity extends from very small systems to systems of enormous scope and that several components are playing a fundamental role, such as time (Bonanno et al., 2011, 2015; Cosco et al., 2017). Based on the figures treated so far and the possible implications related to their interaction, four hypotheses were formulated in order to research the precise outcomes. The details of these formulations and the potential implications have been reported in the following paragraph.

The Current Study

The aim of this study was to highlight the role of different factors, such as personal caregivers' characteristics that are included in the Caregivers Burden Inventory and Resilience Scale for Adults. In order to highlight correlations and dependence relations among the factors mentioned above, the following hypotheses stated:

Hp-1: We hypothesize that the caregivers' personal characteristics (age, years of study, days of work per week, hours of work per week, and years of work) are significantly correlated to CBI factors (time dependence burden, developmental burden, physical burden, social burden, emotional burden, and CBI total score). In particular, we hypothesize positive (+) relations among all factors, specifically years of study characteristic, known as a protective factor in terms of possible burden outcomes.

Hp-2: We hypothesize that the caregivers' characteristics (age, years of study, says of work per week, hours of work per week, and years of work) are significantly correlated to RSA factors (perception of self, planned future, social competence, structured style, family cohesion, social resources, and RSA Total score), considering the central role of resilience for healthcare professionals and the weight of long time assistance activities.

Hp-3: We hypothesize that the CBI factors (time dependence burden, developmental burden, physical burden, social burden, emotional burden, and CBI total score) are significantly correlated to RSA factors (perception of Self, planned future, social competence, structured style, family cohesion, social resources, and RSA Total score) with a particular reference to the possible distinctions among conceptual differences and the role of time in the caregivers' experiences.

Hp-4: We hypothesize the existence of significant dependencies with reference to the two selected predictors, namely, age and gender, and CBI factors (time dependence burden, developmental burden, physical burden, social burden, emotional burden, and CBI total score), highlighting the causal role of age and gender in developing burdens related to health professionals.

MATERIALS AND METHODS

Procedure and Participants

The observation group consisted of 210 participants, 55 males (26,2%) and 155 females (73,8%). The participants' age included in the study was between 18 and 30 years old, with a mean age of 25.92 years old ($SD = 3.33$).

The research was carried out in the University Hospital G. Martino of Messina. The subjects were selected on the basis of their work activities. It has been possible to involve 210 caregivers in order to administrate the complete protocol. Every participant fully completed the questionnaires, including information regarding their work activity, gender, and age.

The compilation of the questionnaires was in online form. Each participant, before adhering to 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 (University of Messina COSPECS Ethical Committee, Ethical committee number: COSPECS_11_2020).

Statistical Analysis

The 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 correlations among variables of the following instruments.

Multivariate linear regression was used to assess the dependence of each burden-related outcome (time dependence, developmental burden, physical burden, social burden, emotional burden, and Total CBI score) on a set of independent predictors (age and gender).

Statistical analyses were performed using the SPSS 26.0 for Windows package.

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

Instruments

Caregivers Burden Inventory

The "Italian version of the Caregiver Burden Inventory" (CBI) (Novak and Guest, 1989), a 24-item multidimensional questionnaire that measures the caregiver's burdens along five dimensions: time dependence, developmental, physical, social, and emotional, was evaluated using a "five-point Likert" scale from 0 (not at all disruptive) to 4 (very disruptive). Several studies examined the reliability both for the total scale and the different factors. In particular, in a recent study by Greco et al. (2017), the CBI was administrated to a sample of Italian caregivers. In the study, the Cronbach's alphas were, respectively, 0.96 for the total scale, 0.91 for time dependence, 0.92 for developmental burden, 0.88, 0.89, and 0.93 for physical, social, and emotional burden. In a second study published by Conti et al. (2019), the total score index was 0.91 and ranging from 0.76 to 0.91 for the abovementioned factors.

Resilience Scale for Adults

The Resilience Scale for Adults (RSA) is a self-report scale based on 33 items, measuring the protective factors related to resilience in adults (Hjemdal et al., 2001; Friborg et al., 2003, 2005; Capanna et al., 2015). As reported by Bonfiglio et al. (2016). The original structure of the RSA includes six factors related to both personal (personal strength, planned future, social competence, and structured style) and external factors (Friborg et al., 2005; Hjemdal et al., 2006; family cohesion and social resources). As reported by Hjemdal et al. (2001), the final version presents a six-factor solution including factors named: (1) Perception of self (Cronbach's $\alpha = 0.74$), (2) Planned future ($\alpha = 0.73$), (3) Social competence ($\alpha = 0.83$), (4) Structured style ($\alpha = 0.80$), (5) Family cohesion ($\alpha = 0.80$), and (6) Social resources ($\alpha = 0.74$). The alphas of the total scale were ranged between 0.82 and 0.95, including the original version and the subsequent adaptations (Friborg et al., 2005; Hjemdal et al., 2006).

RESULTS

Descriptive statistics (the mean and the standard deviation) are reported in **Table 1**, in order to highlight the presence of the considered phenomena.

TABLE 1 | Descriptive statistics for study variables.

	Mean	Standard deviation
Years of study	14.94	2.69
Days of work per week	5.34	1.17
Hours of work per week	36.47	19.22
Years of work	3.68	3.97
Time dependence burden	9.16	5.49
Developmental burden	5.58	5.17
Physical burden	4.44	3.82
Social burden	3.90	4.34
Emotional burden	2.68	4.27
CBI total score	25.77	16.98
Perception of self	17.89	2.46
Planned future	12.14	2.09
Social competence	17.62	2.43
Structured style	11.79	1.87
Family cohesion	18.93	2.90
Social resources	19.30	2.72
RSA total score	97.68	8., 56

Hypothesis 1

Hypothesis 1 concerned the relationships between subjects' work variables and different types of burden. The significant associations between the personal components and the maladaptive outcomes of the different types of burden were hypothesized (see **Table 2**).

In particular, the correlation analysis included age, years of study, days of work per week, hours of work per week, and years of work (total as a caregiver) as caregivers' work variables. In terms of burden, the values of each individual burden type were considered, as time dependence, developmental, physical, social, and emotional burden, and total CBI score.

Going in order, the first personal variable considered was age. Several significant correlations emerged. A significant and positive relationship emerged between age and time dependence, showing how advancing age had the same direction of developing temporal difficulties. Precisely, the direction of increasing age corresponded to an increase in temporal burden. Similarly, age indicated its increase as corresponding to the significant rise in developmental and physical burdens. The three components were significantly and positively correlated with age. Finally, the total score expressed the same direction as the already mentioned components. A significant and positive correlation emerged between age and the total score of the Caregivers Burden Inventory.

Years of study of caregivers represent the second personal variable taken into consideration. It is possible to immediately notice that the years of study could represent a protection factor for the caregivers since all the significant correlations were of a positive sign. This applied to time dependence, developmental burden, social burden, and the CBI total score. These newly expressed relationships showed significant and negative directions; therefore, as the years of caregivers' study grew, there was a decrease in the single burden scores and the total score.

In line with what emerged for age, the variables "days of work per week," "hours of work per week," and "years of work" showed significant and positive relationships with the burdens (single factors and total score). Concerning the first factor, the meaningful relationships of days of work per week were those with time dependence, developmental burden, and with the total score (CBI total score). The number of working days per week increased; there were higher scores in terms of time-related burden, developmental burden, and in general terms (CBI total score). The significant relationship for working hours was with developmental burden, demonstrated by how many hours of work per week corresponded to the sense of failure of caregivers' personal prerogatives.

TABLE 2 | Correlation coefficients among personal-work variables and CBI factors.

	Age	Years of study	Days of work per week	Hours of work per week	Years of work
Time dependence burden	**0.237****	**−0.179****	**0.182****	0.091	0.093
Developmental burden	**0.190****	**−0.164***	**0.224****	**0.160***	**0.225****
Physical burden	**0.163***	**−0.072**	0.068	0.091	0.107
Social burden	−0.030	**−0.151***	0.088	0.084	0.079
Emotional burden	−0.046	−0.082	−0.079	0.009	−0.040
CBI total score	**0.153***	**−0.209****	**0.173***	0.129	**0.138***

*$p < 0.05$ *(two-tailed).*
**$p < 0.01$ *(two-tailed).*
Bold values were the significant values.

In terms of years of work, significant relationships with the developmental burden and the total score were found. The interesting data emerged in systematic terms, referred precisely as developmental burden, that pathological outcome corresponds to the sense of failure of one's personal hopes and life expectations. The general trend was, in fact, positive with all variables, except with years of study (already meant as a protective factor).

As already clarified, it appeared that the years of education and study of the caregivers corresponded to an opposite direction of burden development. In the case of the sense of failure for personal ambitions, however, the data are indicative of the positive relationship between the increase in work commitment and maladaptive outcomes.

Hypothesis 2

Hypothesis 2 and as shown in **Table 3**, several significant correlations were found among caregivers' personal variables and resilience factors. Starting from age, three negative and significant correlations emerged, respectively, with perception of self, structured style, and family cohesion.

These relations indicated that the increase in age corresponded to a decrease in the general perceived confidence about subjects' efficacy, abilities, and positive outlook. In the same direction, the other two negative relations pointed out the decrease of a structured style and family cohesion, indicating goal-orientated activities and shared family values, enjoyment of situations, and a collective optimism for family-orientated perspectives.

The positive correlation that emerged as significant was with planned future, highlighting a growing sense of belief about possible opportunities and future perspectives. Years of the study appeared to be in a positive relationship with both perception of self and family cohesion, indicating a common direction of the years of education with the general self-perceived range of abilities and possibilities, together with enjoyable family figures.

Days of work per week showed a significant and positive relationship with planned future, social resources, and RSA total score, indicating similar orientations. Contrary to this latter point, the perception of self emerged in inverse relation, so that caregivers' personal beliefs about self-efficacy and abilities seemed to decrease in relation to the increase in days of work.

Hours of work per week showed a significant and positive relationship with planned future, while years of work had two inverse and significant correlations with perception of self and structured style, to properly mark the impact of a long work commitment on self-efficacy and planned activities.

Hypothesis 3

As shown in **Table 4**, positive correlations were found among CBI and RSA variables, with a particular reference to two strong domains, namely, planned future and social resources. The first reference is due to the perception of self, showing two significant and inverse correlations with developmental burden and the Caregiver's Burden Inventory total score. In detail, the prerogatives related to the caregiver's sense of self-efficacy emerged as inverted with the possibility to develop an understanding of failure linked to personal hopes and ambitions. The general score indicated the same direction as that of self-efficacy, and personal representations about general and specific abilities show themselves as opposite to burdens and vice versa. Planned future was involved in several and interesting relations, all positive and significant. All CBI factors emerged indicating directions with positive outlooks, beliefs, and the necessity to plan for the future. Social resources were in positive and significant correlations, respectively, with time dependence burden, developmental burden, physical Burden, and the CBI total score.

Hypothesis 4

To study dependence relations, as reported in **Table 5**, age and gender effects were involved as independent variables and predictors in their relationships with CBI variables. As emerged through the analysis, significant causal relations emerged among variables. About age, three relations were highlighted, respectively, with time dependence, developmental burden, and physical burden. These relations explained the relevant role of age in increasing the possibility to experience burdens. Going in-depth, the burden depending on the time dedicated to clinical assistance resulted in being predictable as a final outcome due to aging, as also for caregivers' belief to be cut off from possible life's opportunities and the presence of physical outcomes. Regarding the effect of gender, significant dependencies were clearly pointed out by the regression analysis, in particular among gender and developmental, social, emotional burden, and CBI total score. Male gender appeared to be a significant predictor of the decrease in the already mentioned outcomes so that all significant relationships were negative. These data referred to the limitations coming from the excessive assistance activities,

TABLE 3 | Correlation coefficients among personal-work variables and RSA factors.

	Age	Years of study	Days of work per week	Hours of work per week	Years of work
Perception of self	−**0.115****	**0.097***	−**0.106****	−0.038	−**0.092***
Planned future	**0.105****	−0.057	**0.205****	**0.100****	0.037
Social competence	0.041	−0.025	0.041	0.037	−0.023
Structured style	−**0.092***	−0.082*	−0.037	−0.015	−**0.137****
Family cohesion	−**0.087***	**0.081***	−0.013	0.020	−0.029
Social resources	0.065	−0.061	**0.127****	−0.001	−0.005
RSA total score	−0.012	−0.010	**0.084***	0.059	−0.053

*$p < 0.05$ *(two-tailed).*
**$p < 0.01$ *(two-tailed).*
Bold values were the significant values.

TABLE 4 | Correlation coefficients among CBI and RSA variables.

	Perception of self	Planned future	Social competence	Structured style	Family cohesion	Social resources	RSA total score
Time dependence burden	−0.068	**0.174****	−0.002	−0.074	−0.074	**0.089***	0.014
Developmental burden	−**0.117****	**0.308****	0.047	−0.005	0.002	**0.130****	**0.118****
Physical burden	−0.064	**0.300****	0.054	−0.056	−0.028	**0.093***	**0.083***
Social burden	−0.059	**0.205****	−0.043	0.009	−0.053	0.026	0.060
Emotional burden	−0.040	**0.155****	0.070	0.006	−0.001	0.014	0.067
CBI total score	−**0.099***	**0.297****	0.028	−0.037	−0.037	**0.102****	**0.085***

*$p < 0.05$ *(two-tailed).*
**$p < 0.01$ *(two-tailed).*
Bold values were the significant values.

TABLE 5 | Multivariate linear regressions analysis.

	Age		Gender	
	B (CI)	*P*	B (CI)	*p*
Time dependence burden	0.377 (0.147/0.608)	**0.001***	−0.,202 (−1.872/1.468)	0.812
Developmental burden	0.241 (0.032/0.451)	**0.024***	−1.997 (−3.517/−0.477)	**0.010***
Physical burden	0.177 (0.014/0.339)	**0.033***	−0.858 (−2.035/0.320)	0.152
Social burden	−0.047 (−0.230/0.136)	0.614	−2.230 (−3,554/−0.906)	**0.001***
Emotional burden	−0.140 (−0.324/0.044)	0.134	−1.847 (−3,180/−0.514)	**0.007***
CBI total score	0.608 (−0.098/1.315)	0.091	−7.133 (−12.250/−2.016)	**0.007***

B, beta coefficient; CI, confidence interval. *$p < 0.05$ *was considered as significant for the multivariate linear regression analyses.*

social and emotional outcomes, and the general possibility to develop burden.

DISCUSSIONS

Our study was aimed at highlighting the existing relations among different factors, such as the personal characteristics of the caregivers and the variables referred to as burdens and resilience. In the various sections of the results, different hypotheses have been presented, and the analysis has highlighted many significant relationships. In particular, the study showed two classes of research, oriented to the detection of correlations and causality relationships. The comparison between the caregivers' characteristics and the factors of the reference domains, represented a useful occasion for the comparison between the emerged results, current, and previous literature. The analysis, therefore, considered factors such as age and gender of the caregivers, together with their attitude to work (in a temporal sense) and educational years. The choice to compare these variables with those of the abovementioned domains mainly depended on the fact that the courses related to these healthcare professions were activated in our university.

This university opening is part of the logic that various authors followed regarding clinical efforts. With particular reference to clinical practice, our orientation corresponds to the current needs and challenges in the field of clinical psychology (Caputo, 2013; Carrozzino et al., 2019; Conversano, 2019; Martino et al., 2019b;

Merlo, 2019a,b; Settineri et al., 2019d). The results obtained through the analysis, starting from the question of burden, highlighted some fundamental facts. The age of the caregivers always explained positive directions with the burdens identifying specific issues. What appeared opposed to the increase in the age of the caregivers was precisely the ability to plan the future and manage time, which refers to the personal life of the caregivers. The same directions were taken by the developmental burden, and therefore addressed to personal ambitions and possibilities of self-realization and extended to physical and general issues.

As stated by Win et al. (2017), according to Lim et al. (2014), some data emerge in close relationship with the burden in the field of performance. In both contributions, the authors noted changes in the caregivers' performance with reference to age. The first contribution cited statistically ascertained significant differences, suggesting the central role of age with reference to worrying feelings. All of these clearly affect the performance of healthcare professionals. If, on the one hand, the younger caregivers experience the feeling of worry about work activities, on the other hand, the older caregivers instead experience high levels of burden and fatigue.

This datum could be extended to other variables considered in terms of work commitment, therefore the years of study, hours, and days of work per week. The significant relationships highlighted congruent directions between the development of the burdens and the increase in work commitment. As supported by Stanley et al. (2017), the outcomes of exposure to difficult existential conditions bring outcomes to the mental and physical health of caregivers (Mitsonis et al., 2012; Suro and Weisman de Mamani, 2013; Gater et al., 2014; Gupta et al., 2015; Stanley et al., 2016). The literature just mentioned opens the dialogue about the issue of interventions and education of caregivers. We referred to specific educational programs for university courses.

Our results revealed a significant and negative correlation between the years of study of the caregivers and the different types of burden, including time dependence, developmental burden, social burden, and the overall scores. The occupational and educational question of caregivers has long been discussed (Toth-Cohen, 2000), and several authors treated the need for specific educational and support programs for caregivers and family members (Ji et al., 2014). The result to which we refer indicated a decrease in the development of the aforementioned burdens, followed by the increase in the years of education. This result was in line with recent scientific contributions (Greene and Monahan, 1989; Lee and Kim, 2017; Mukherjee, 2017; Batra et al., 2018; Cianfrocca et al., 2018; Conant, 2019; Hekmatpou et al., 2019).

In terms of risk and protection factors, it is well-known that different personal and environmental characteristics affect the life of the healthcare professionals (Haley et al., 2003; Lovell et al., 2012a,b; Dardas and Ahmad, 2014; Bekhet and Matel-Anderson, 2017). Among the various factors involved, according to the current state of the art, it is possible to identify particularly adaptive trends for caregivers (Pagnini et al., 2016), which allowed us to consider basilar factors as in the case of resilience. According to Palacio et al. (2018), factors such as resilience, perceived competence, emotional regulation, and positive aspects of care represent fundamental points for the caregivers' health conservation.

In terms of resilience, our results highlighted specific trends, so that starting with the age increase in the caregivers, there was a decrease in self-perceptions, adaptive styles, and family cohesion. Conversely, qualities such as planning for the future appeared to be inversely related. The years of education and professional training took directions akin to the ability to remain adherent to an adaptive self-perception and a cohesive family. The variables related to work commitment in the week, in the month, and in general had several significant correlations. In detail, the perception of self always appeared negatively associated with variables, but rather for years of study. The overall years of work showed a negative relationship with the structured style, indicative of a decrease in containment and coping capacity. Several studies have been previously mentioned, indicating the relationships between variables related to burdens experienced by caregivers and resilience factors. In our results, the relationships that immediately appeared strongly correlated concerned the relationship of planned future with all burdens. Positive and significant relationships emerged, certainly guaranteeing to understand the temporal dynamics of the caregivers.

Several studies previously mentioned indicated the relationships between variables related to burdens experienced by caregivers and resilience factors. In our results, the relationships that immediately appeared strongly concerned about the relationship of the planned future variable with all burdens. Positive and significant relationships emerged, certainly guaranteeing the comprehension with reference to the temporal dynamics of the caregivers. The "cost of caring" is a concept that manifests itself through issues on future planning (Wang and Han, 2019), with greater prevalence in the caregivers of patients with particularly serious medical conditions. In the study of the factors affecting these limitations, Walker and Hutchinson (2018) reported the establishment of some barriers that prevented future planning for caregivers. Although the need was apparent, intervening factors appeared exactly as barriers.

The authors reported fundamental studies about these barriers, such as that of Davys and Haigh (2008) indicating the presence of a planning gap due to internal psychological figures. In the same direction, Dillenburger and McKerr (2011) and Stehlik (2000) highlighted the fact of feelings of helplessness, resignation, avoidance, denial, and guilt about not planning. A second relevant dimension was that of uncertainty, so the authors reporting previous articles (Eley et al., 2009; Pryce et al., 2017) showed how the subjects withdrew from the planning phase due to this additive burden. The contribution of Walker and Hutchinson (2018) represents an example of practical analysis, which allows us to understand how relevant the temporal issue is in the life span. Regarding the emergence of other significant relationships, the intersection of the variables of the two scales highlighted positive directions between the burden and the social dynamics of the caregivers. A metanalysis by Parker Oliver et al. (2017) on the social issue and the work commitment of caregivers highlighted fundamental phenomena. Social isolation and the incidence of burdens is usually widespread, and psychosocial outcomes occur at different levels, mental, physical, and social.

The last hypothesis concerned the level of causal incidence of some predictors on burden phenomena. Significant causal relationships identified a primary role for the two predictors, as several results emerged. Age and gender were related significantly to the burdens, to the point that none of the individual burden was excluded from significant relationships. In detail, age had an incident role on the temporal, developmental, and physical burden. Gender was in a relationship of significant dependence with the developmental, social, and emotional burden. The overall score was in a dependence relation with the overall burden factor. In line with some contributions in the literature, the results obtained showed a clear impact of these two dynamics on the possibility of developing burdens in caregivers.

What emerged from the results of this work, referred to the presence of different dynamics, which, respectively, consisted of adverse outcomes due to clinical care and the ability of caregivers to cope with difficulties. The subject of burdens has been treated by many contributions in the literature, some of which have proposed different types of intervention. It is necessary to understand that among the various types of existing caregivers, duly educated professional figures are flanked by informal caregivers. In most cases, caregivers take on the role of family members or relatives who take responsibility for care. Future interventions and perspectives must take account of these dynamics, right from the early educational stages of professionals.

Many of the caregivers have not received specialized education, to the point that they do not have skills useful for dealing with the pathological realities of patients. This figure is also extended to those professional figures who by definition acquire skills during the university training courses (Langher et al., 2014, 2018; Parola and Donsì, 2018, Settineri et al., 2018; Parola and Donsì, 2019; Merlo et al., 2020b; Parola and Felaco, 2020). The success or failure of therapies and treatments often depends on the skills of health professionals, and this suggests that they cannot be overlooked, with particular reference to adult and adolescent medical conditions (Mullen, 1997; Brown, 1999; Lingiardi et al., 2010; Shrivastava et al., 2013; Sugiharto et al., 2017; Di Giuseppe et al., 2019a; Martino et al., 2019a; Rosa et al., 2019, Settineri et al., 2019e; Ardeleanu et al., 2020; Martino et al., 2020; Moroianu et al., 2020; Muzi, 2020; Nedelcu et al., 2020).

Regarding the commitment of informal caregivers, several authors have conducted analyses that, despite the past years, remain effective and well-structured (Yates et al., 1999; Donelan et al., 2002; Pinquart and Sörensen, 2007). As already stated, the research results represent the basis on which the necessary interventions should arise, although educational practices must describe the first step. The fact that these educational gaps currently persist places caregivers in a position to experience adverse outcomes even today (Benson et al., 2020; Campione and Zebrak, 2020; Clancy et al., 2020; Price et al., 2020). The consequences relating to the non-observation of these personal, educational, and institutional needs are manifold and extend even to the defensive, neuropsychological, and neurovegetative sphere (Schredl, 2013; Dell'Osso et al., 2014; Rania et al., 2018; Catalano et al., 2019; De Stasio et al., 2019; Schredl et al., 2019; Settineri et al., 2019b; Di Giuseppe et al., 2020a,b; Hoyt et al., 2020; Romero-Martínez et al., 2020; Somma et al., 2020).

Our experience involved young caregivers, whose commitment in the beginning produce dysfunctional outcomes since the early years of work. This fact highlights two central points, respectively, the need for intervention and the implementation of educational programs for all professionals. One of the merits of this type of research consists in the possibility of explaining the origin and the existing relationships between phenomena that are noticed through valid instruments. Further contributions should take into account a different but, nonetheless, central level with regard to the expression of health and pathological conditions experienced by the caregivers. The potential and function of the narrative of the subjects (Bourlot, 2018, 2020) represent relevant figures in clinical relationships.

The expressive modalities of the subjects are conditioned by approaches which, despite guaranteeing an excellent statistical and population framework, neglect the subjective aspects through which the therapeutic process is carried out.

A substantial set of contents could emerge through narrative analyses, which in most cases escape statistical frameworks and which are expressed through manifestations that mask the real meanings (Bourlot, 2019; Manfredi and Massardi, 2019; Settineri et al., 2019d). The advantage made possible by the current analysis refers to the production of evidence that testifies to general conduct, which compared to the other works present in the literature allows the researchers to orient the resolutive plans of the conditions currently current. In our experience, in fact, the difficulties witnessed by the presence of burdens were accompanied by attitudes of resilience and followed by adaptive and compensatory perspectives. In the future, it will be necessary to envisage variations and changes that comply with the evidence that emerged from the literature and from the commitment of clinicians to the health of patients and those "invisible patients" who dedicate themselves every day to a very particular type of assistance.

IMPLICATIONS OF THE STUDY

In order to highlight relevant dynamics occurring in health professional's experience, two important factors were taken into account. Health professionals and caregivers represent an important category, reflecting unknown phenomena of health sectors. The analyses were based on the selected themes in order to compare well-known dynamics with outcomes related to work. Some considerable results emerged, suggesting how independent factors such as age and gender impact caregivers' professional and private life. The emerged data made it possible to compare our results with previous published research evidence. In these terms, it was possible to make it clear as well-known dynamics were also present in our territory.

The choice to maintain the metaphor "invisible patients" depended on a lack of knowledge on caregivers' difficulties. Our results highlighted a continuity with those contributions that showed the need for a greater knowledge on the treated phenomena. The aim to distinguish the negative outcomes from the positive possibilities, such as resilience, was due to the need to point out adaptive strategies related to prevention and support.

The results that emerged can be considered as evidence on the basis of which future interventions may arise.

LIMITATIONS AND CONCLUSION

This study presents a diversity of limitations that should be overcome in future studies. The number of health professionals employed in public and private realities is high, and subsequent studies should expand the observation group. This would lead researchers to the possibility of extending the data to a more representative population. The number of participants has an evident prevalence of female subjects, and although it is known that the population of caregivers in the area is predominantly female, a gender balance would be necessary. The reference to young caregivers would require more studies to support their relevance and the negative outcomes experienced. Although this latter reference constitutes a limitation, this study was aimed at implementing knowledge about it. The relevant figure was included by the presence of burdens from the early years of experience of the caregivers, accompanied by good resilience skills. This fact can be considered a guarantee of the understanding of the need to operate interventions aimed at assisting health professionals and reducing maladaptive outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical committee of the Department of Cognitive Sciences, Psychology, Educational and Cultural Studies (COSPECS), University of Messina, Italy Ethical committee number: COSPECS_11_2020. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

EM made a significant contribution to design the research study, draft the manuscript, revised it critically, also performing the statistical analysis, and providing the interpretation of data. IM and AS made a significant contribution to design and revise the research study. SS gave the final approval. All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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BRIEF RESEARCH REPORT
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Personality Disorder and Physical Health Comorbidities: A Link With Bone Health?

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We examined whether personality disorders (PDs) (any, cluster A/B/C) were associated with bone mineral density (BMD) in a population-based sample of Australian women ($n = 696$). Personality and mood disorders were assessed using semi-structured diagnostic interviews. BMD was measured at the spine, hip, and total body using dual-energy x-ray absorptiometry (GE-Lunar Prodigy). Anthropometrics, medication use, physical conditions, and lifestyle factors were documented. The association between PDs (any, cluster A/B/C) and BMD (spine/hip/total body) was examined with multiple linear regression models. The best models were identified by backward elimination including age, weight, physical activity, smoking status, alcohol consumption, dietary calcium intake, mood disorders, physical multimorbidity, socioeconomic status, and medications affecting bone. The variables were retained in the model if $p < 0.05$. All potential interactions in final models were tested. Those with cluster A PD, compared to those without, had 6.7% lower hip BMD [age, weight adjusted mean 0.853 (95% CI 0.803–0.903) vs. 0.910 (95% CI 0.901–0.919) g/cm^2, $p = 0.027$] and 3.4% lower total body BMD [age, weight, smoking, alcohol, calcium adjusted mean 1.102 (95% CI 1.064–1.140) vs. 1.139 (95% CI 1.128–1.150) g/cm^2, $p = 0.056$]. No associations were observed between cluster B/C PDs and hip/total body BMD or between any of the PD clusters and spine BMD. To our knowledge, this study is the first to investigate the bone health of women with PD in a population-based sample. Given the paucity of literature, replication and longitudinal research including the examination of underlying mechanisms and sex differences are warranted.

Keywords: comorbidity, personality disorder, psychiatry, physical health, medical condition, bone

INTRODUCTION

Emerging early in the life span, a personality disorder (PD) presents as enduring patterns of maladaptive thinking, emotional and inner experiences, and behaviors—causing significant distress and impairment (1). PDs have traditionally been conceptualized as 10 distinct disorders that are organized within three clusters: A, "odd-eccentric" features; B, "dramatic/emotional/erratic" features; and C, "anxious/fearful" features (1).

Growing evidence points to adverse physical health comorbidities among people with PD, including chronic physical, pain, and sleep conditions (2, 3)—however, little is known regarding the factors underlying these associations (2). PD also appears to be associated with musculoskeletal problems (2, 3); however, there is a paucity of research examining the underlying bone health of people with PD.

Psychological/behavioral factors including impulsivity and self-sabotaging type behaviors, which are typical of "cluster B" symptomatology, appear to lead to difficulties with general health treatment compliance (4) and thus plausibly influence the physical health of people with these PDs. Biological/other health-related factors are suggested to include (but may not be limited to) multiple and long-term poor health-related lifestyle choices and medication use (5, 6) and metabolic syndrome (3). However, little is known whether different PD clusters (i.e., different presentations of PD symptomatology) are independently associated with poorer bone health compared to people without PDs.

Kahl et al. (7, 8) conducted the first clinical-based studies showing that comorbid borderline PD (a cluster B PD) and depressive disorders were associated with reduced bone mineral density (BMD) in younger women. Yet, there are no studies from the population-based setting or across the wider adult age range. Therefore, we explored direct associations between PD and BMD in a large population-based sample of Australian women—exploring the role of age, anthropometrics, lifestyle factors, multimorbidity, medication use, and mood disorders.

MATERIALS AND METHODS

This study examined data from women participating in the population-based Geelong Osteoporosis Study (GOS) in Australia (9). Originally, 1,494 women (response rate 77.1%) were randomly selected from the electoral rolls for the Barwon Statistical Division during 1994–1996. Complete details have been published elsewhere (9–11). We utilized data collected from participants who returned for assessment during 2011–2014. Participants who did not complete a psychiatric assessment ($n = 80$), had missing BMD data ($n = 50$), or with multiple PD clusters ($n = 22$) were excluded. This study consisted of $n = 696$ women aged ≥28 years. Barwon Health Human Research Ethics Committee approved the study, and written informed consent was obtained from all participants.

Areal BMD (g/cm^2) was measured at the posterior–anterior (PA) spine (L2–4), femoral neck (hip), and total body including head using dual-energy X-ray absorptiometry (Prodigy; GE Lunar, Madison, WI, USA). Technicians carried out all examinations and performed daily calibrations of the densitometer with equipment-specific phantoms. Osteoporosis was determined by a BMD T-score of <-2.5 at the spine and/or hip (12).

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM) Axis I Disorders, non-patient edition (SCID-I/NP) identified lifetime mood disorders [i.e., major depressive disorder (MDD), minor depression, bipolar disorder, dysthymia, mood disorders due to a general medical condition, and substance-induced mood disorder] (13). The Structured Clinical Interview for DSM-IV Axis II personality disorders (SCID-II) identified PDs (14). Consistent with the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the 10 PDs were categorized into three clusters: cluster A PDs (i.e., schizoid, paranoid, and schizotypal PDs); cluster B PDs (i.e., antisocial, borderline, narcissistic, and histrionic PDs); and cluster C PDs (i.e., avoidant, dependent, and obsessive–compulsive PDs) (1). As previously published, all interviews were conducted by trained personnel with post-graduate qualifications in psychology (10).

Weight and height were measured to the nearest 0.1 kg or 0.1 cm, respectively. Current smoking and mobility were self-reported. Participants were deemed active if vigorous or light exercise was performed regularly; otherwise, participants were classified as sedentary. Alcohol consumption and calcium intake were estimated from a validated food frequency questionnaire (15). Current medication use affecting bone was recorded, including antiresorptive agents (bisphosphonates/selective estrogen receptor modulators), oral hormone replacement therapy, oral glucocorticoids, and antidepressants. Participants brought lists of medications or containers to the assessment to ensure accurate recordings. Participants self-reported the presence of physical conditions. These were confirmed by medical record, medication use, or clinical data, where possible, and included arthritis, cardiovascular disease, thyroid disorders, metabolic disorders, gastrointestinal disease, gastroesophageal reflux disease, syncope and seizures, recurrent headaches, pulmonary diseases, psoriasis, liver diseases, and cancers (16). Utilizing these data, we defined physical multimorbidity as the presence of ≥5 lifetime physical health disorders (17, 18). Area-based socioeconomic status (SES) was determined using the Index of Relative Socio-economic Advantage and Disadvantage (IRSAD). A lower score (Quintile 1) indicated greater disadvantage; a higher score, greater advantage (Quintile 5) (9).

Statistical analyses were performed using Minitab (version 18). Group differences were determined using *t*-tests for parametric variables, Kruskal–Wallis for nonparametric continuous variables—for discrete variables, chi-square tests

Abbreviations: BMD, bone mineral density; CI, confidence interval; DSM, Diagnostic and Statistical Manual of Mental Disorders; IRSAD, Index of Relative Socio-economic Advantage and Disadvantage; MDD, major depressive disorder; PD, personality disorder; SCID-I/NP, The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders Axis I Disorders, non-patient edition; SCID-II, The Structured Clinical Interview for DSM-IV Axis II personality disorders; SES, socioeconomic status.

TABLE 1 | Characteristics of all and those with and without a PD.

	All $n = 696$	PD $n = 131$	No PD $n = 565$	p^*
Age (years)	56.2 (42.6–67.6)	52.2 (38.7–63.8)	57.1 (43.3–68.8)	0.012
Weight (kg)	71.5 (62.2–83.8)	77.0 (65.6–87.9)	70.1 (61.9–82.6)	0.003
Height (m)	1.62 ± 0.06	1.63 ± 0.07	1.62 ± 0.06	0.274
Smoking (current)	78 (11.4%)	18 (14.1%)	60 (10.8%)	0.291
Mobility (active)	507 (74.2%)	83 (65.4%)	424 (76.3%)	0.011
Alcohol intake (g/day)	2.2 (0.3–11.9)	1.8 (0.4–7.8)	2.4 (0.3–13.1)	0.527
Calcium intake (mg/day)	824 (637–1,037)	821 (597–1,089)	826 (640–1,032)	0.901
Mood disorder (lifetime)	255 (36.6%)	78 (59.4%)	177 (31.3%)	<0.001
Physical multimorbidity (lifetime)	115 (16.5%)	29 (22.1%)	86 (15.2%)	0.055
Socioeconomic status				0.637
Quintile 1 (lowest)	103 (14.8%)	23 (17.6%)	80 (14.2%)	
Quintile 2	76 (10.9%)	16 (12.2%)	60 (10.6%)	
Quintile 3	269 (38.7%)	46 (35.1%)	223 (39.5%)	
Quintile 4	135 (19.4%)	28 (21.4%)	107 (18.9%)	
Quintile 5	113 (16.2%)	18 (13.7%)	95 (16.8%)	
Medication use (current)				
Antiresorptive agents	21 (3.0%)	3 (2.3%)	18 (3.2%)	0.589
Glucocorticoids	20 (2.9%)	4 (3.1%)	16 (2.8%)	0.778
Hormone therapy	26 (3.7%)	3 (2.3%)	23 (4.1%)	0.333
Antidepressants	114 (16.4%)	32 (24.4%)	82 (14.5%)	0.006
Unadjusted BMD (g/cm^2)				
Spine	1.20 ± 0.18	1.22 ± 0.18	1.20 ± 0.18	0.306
Hip	0.92 ± 0.14	0.94 ± 0.14	0.92 ± 0.14	0.048
Total body	1.14 ± 0.11	1.16 ± 0.11	1.13 ± 0.11	0.055
Osteoporosis (current)	57 (8.2%)	8 (6.1%)	49 (8.7%)	0.335

Values are given as median (interquartile range), mean ± standard deviation or n (%).
**Comparing women with and without PD.*
BMD, bone mineral density; PD, personality disorder.

or Fisher's exact test when expected cell counts were less than five. The association between PD (any, cluster A/B/C) and BMD (spine/hip/total body) was examined with multiple linear regression in unadjusted models (Model I) and "best models" (Model II). The best models were identified by backward elimination including age, weight, physical activity, smoking status, alcohol consumption, dietary calcium intake, mood disorders, physical multimorbidity, SES, and medications affecting bone (*c.f.* above). The variables were retained in the model if $p < 0.05$. All potential interactions in final models were tested.

RESULTS

Of 696 women, 131 (18.8%) met the criteria for a PD. Women with PD were more likely to be younger, heavier, sedentary, use antidepressants, had a lifetime mood disorder, and had higher hip and total body BMD than those without PD (all $p < 0.05$); otherwise, the groups were similar (**Table 1**).

After age, weight adjustments, no differences were detected in spine, hip, or total body BMD between those with and without any PD (all $p > 0.05$).

The frequency of PD clusters was: 2.7%, cluster A ($n = 19$); <1%, cluster B ($n = 5$); and 15.4%, cluster C ($n = 107$).

Unadjusted and best models showing associations between PD clusters and BMD are presented in **Table 2**. Those with cluster A PD, compared to those without, had 6.7% lower hip BMD [age, weight adjusted mean 0.853 (95% CI 0.803–0.903) vs. 0.910 (95% CI 0.901–0.919) g/cm^2, $p = 0.027$] and 3.4% lower total body BMD [age, weight, smoking, alcohol, calcium adjusted mean 1.102 (95% CI 1.064–1.140) vs. 1.139 (95% CI 1.128–1.150) g/cm^2, $p = 0.056$]. No differences were detected in spine BMD between those with and without cluster A PD. Finally, no differences were detected in spine, hip, and total body BMD for those with and without cluster B or C PDs.

DISCUSSION

To our knowledge, this study is the first to investigate bone health of women with PD in a population-based sample. It showed that those with cluster A PD have lower hip/total body BMD than those without. There were no associations between pooled PDs, cluster B or cluster C PD and BMD at any site.

TABLE 2 | Unadjusted and best models presenting associations between PD clusters and BMD using multiple regression.

BMD site	PD status	Model I: unadjusted			Model II: best model*		
		B	SE	*p*	*B*	SE	*p*
Spine	Cluster A	0.034	0.043	0.435	−0.010	0.039[b]	0.789
	Cluster B	0.026	0.083	0.756	−0.025	0.083[b]	0.761
	Cluster C	0.013	0.019	0.499	−0.005	0.018[b]	0.769
Hip	Cluster A	−0.007	0.033	0.834	−0.057	0.026[a]	0.027
	Cluster B	0.006	0.064	0.922	−0.023	0.050[a]	0.645
	Cluster C	0.034	0.015	0.027	0.009	0.012[a]	0.428
Total body	Cluster A	0.009	0.025	0.724	−0.037	0.019[c]	0.056
	Cluster B	−0.021	0.049	0.675	−0.052	0.041[d]	0.202
	Cluster C	0.023	0.011	0.045	0.005	0.009[e]	0.599

**Best models, adjusted for [a]age and weight; [b]age, weight, and alcohol; [c]age, weight, smoking, alcohol, and calcium intake; [d]age, weight, smoking, and alcohol; [e]age, weight, activity, and smoking.*

B, regression coefficient; BMD, bone mineral density; SE, standard error; PD, personality disorder.

Kahl et al. (7, 8) suggested that young women with borderline PD and current major depression may be a group at risk of developing osteoporosis. In their clinical study, the BMD of 24 women with MDD, 16 with borderline PD, 23 with MDD and comorbid borderline PD, and 20 healthy control participants were compared (7). The MDD only group were further divided into younger/older age groups [mean age 30 years (MDD30); 43 years (MDD43), respectively]. Women with MDD and comorbid borderline PD had significantly lower BMD at the lumbar spine compared with women with borderline PD alone and the younger women with MDD (MDD30) (7). No significant associations were reported between the groups at the other sites (i.e., right and left femur and forearm of non-dominant hand) (7). Markers of bone turnover were also measured, and compared with healthy control participants, elevated levels of osteocalcin were reported among women with MDD and borderline PD group (7). However, C-terminal degradation products of type I collagen (CTx) were highest among the MDD43 group, and tumor necrosis factor-α, interleukin-6, and osteoprotegerin were highest among the MDD30 group (7). To summarize, they postulated that rather than the presence of borderline PD alone, the acuteness of a co-occurring MDD may contribute to bone loss through associated immune/endocrine disturbances (7, 8). Though not directly comparable, we detected no direct association between cluster B and BMD. However, the lack of associations between cluster B PD and BMD detected in the present study could also be due to power constraints.

The novelty of the current research precludes meaningful comparisons with other studies on cluster A/C in relation to bone health. It is possible that psychological/social factors/processes that are characteristic of cluster A PDs, including enduring social isolation and avoidance coping, may be a barrier to engaging with healthcare providers for preventative, ongoing monitoring of physical health and/or engagement with treatments (2, 19)—including bone health. It is also plausible that vitamin D intake could be a biological mechanism underlying the associations.

In terms of study limitations, power limitations prevented analyses investigating specific PDs, other psychiatric disorders, and underlying biological mechanisms. Specifically, we did not collect and, therefore, did not examine the role of vitamin D, which is a known regulator of bone and mineral metabolism, as a confounder/moderator of associations between PD and BMD. This may be an area that warrants further research, given the suggestion that vitamin D may play a role in the manifestation of reduced quality of life *via* poorer health status among postmenopausal women referred for evaluation for osteopenia/osteoporosis (20) and, separately, with poorer psychological and somatic symptomatology (21). We also acknowledge that the classification of PD is undergoing significant reform, and dimensional measures of personality were not examined. Strengths of this study include the wide adult age range, gold standard tool for assessing psychiatric disorders, and adjustment for many known confounders.

Our preliminary study supports an association between PD and bone health. A more substantive evidence base is needed to further uncover the clinical implications of a relationship between PD and bone health. It may be important to determine whether monitoring the bone health of people with PD and comorbidities is warranted, given polypharmacotherapy is often prescribed for the treatment of PD (22), and specific agents, such as selective serotonin reuptake inhibitors, anticonvulsants, and antipsychotics, are associated with decreased bone mass and increased risk for osteoporosis and related fractures (23). This may require a coordinated effort between primary and endocrinological care, given indications that psychological/behavioral symptoms of PD may be a barrier to general health treatment/compliance for some individuals (4).

Given the paucity of literature, replication and longitudinal research including the examination of underlying mechanisms and sex differences are warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Barwon Health Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LW conceived and designed the study. LW and AS performed the analyses. All authors contributed to the interpretation of the data and drafting of the article, provided critical revisions to the article, and approved the final version to be published.

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A Scientometric Review of Alexithymia: Mapping Thematic and Disciplinary Shifts in Half a Century of Research

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The term "alexithymia" was introduced in the lexicon of psychiatry in the early '70s by Sifneos to outline the difficulties manifested by some patients in identifying and describing their own emotions. Since then, the construct has been broadened and partially modified. Today this describes a condition characterized by an altered emotional awareness which leads to difficulties in recognizing your own and others' emotions. In half a century, the volume of scientific products focusing on alexithymia has exceeded 5,000. Such an expansive knowledge domain poses a difficulty for those willing to understand how alexithymia research has developed. Scientometrics embodies a solution to this issue, employing computational, and visual analytic methods to uncover meaningful patterns within large bibliographical corpora. In this study, we used the CiteSpace software to examine a corpus of 4,930 publications on alexithymia ranging from 1980 to 2020 and their 100,251 references included in Web of Science. Document co-citation analysis was performed to highlight pivotal publications and major research areas on alexithymia, whereas journal co-citation analysis was conducted to find the related editorial venues and disciplinary communities. The analyses suggest that the construct of alexithymia experienced a gradual thematic and disciplinary shift. Although the first conceptualization of alexithymia came from psychoanalysis and psychosomatics, empirical research was pushed by the operationalization of the construct formulated at the end of the '80s. Specifically, the development of the Toronto Alexithymia Scale, currently the most used self-report instrument, seems to have encouraged both the entrance of new disciplines in the study of alexithymia (i.e., cognitive science and neuroscience) and an implicit redefinition of its conceptual nucleus. Overall, we discuss opportunities and limitations in the application of this bottom-up approach, which highlights trends in alexithymia research that were previously identified only through a qualitative, theory-driven approach.

Keywords: alexithymia, co-citation analysis, affect regulation, science mapping, citespace, systematic review, emotional processing, scientometric review

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INTRODUCTION

The word "Alexithymia" stems from old Greek and literally means "without words for emotions" ["a"=lack + "lèxis"=word + "thymos"=mood or emotion, see Lesser (1)]. This term describes a personality construct characterized by a deficit in emotional awareness and was firstly introduced at the beginning of the 70s by Peter Sifneos [cf. e.g., (2)] to denote the particular characteristics of people suffering from a variety of psychosomatic diseases (i.e., ulcerative colitis, asthma, peptic ulcer, rheumatoid arthritis). Indeed, the observations conducted on similar patients revealed that their physical symptoms were accompanied by a general inability to verbalize their emotions which prevented them from successfully engaging in a talking therapy. Even though the symptoms were related primarily to the patient's capacity to express their emotions through words, Sifneos et al. realized that the linguistic problem was only the surface of a deeper underlying issue. The main features of alexithymia they identified were chiefly: (i) difficulty in identifying feelings and distinguishing between feelings and bodily sensations of emotional arousal; (ii) difficulty in describing feelings to others; (iii) externally oriented thinking; and (iv) limited imaginal capacity (3).

In a short time, this psychological construct captured the attention of a number of researchers within the psychiatric community interested in the treatment of psychosomatic diseases. Indeed, in 1976, alexithymia was the main theme of the 11th European Conference on Psychosomatic Research (ECPR) held in Heidelberg, Germany (4). After a brief period in which alexithymia was hypothesized to identify a specific type of psychopathological personality with categorical characteristics (i.e., a nosological category) positively correlated with psychosomatic disorders, it became clear that alexithymia is instead a personality trait with dimensional and multifactorial characteristics which is shared also by other clinical populations (5). Alexithymia was also found to be normally distributed in the general population (6, 7), further confirming the continuous nature of the construct.

The search for a more precise definition of this construct was accompanied by the need to identify reliable instruments for its assessment. First of all, Sifneos developed the Beth Israel Hospital Questionnaire (BIQ; 2); shortly thereafter with a colleague, he put forward the Schalling-Sifneos Personality Scale (8, 9). At the beginning of the 1980s, Kleiger and Kinsman (10) proposed the MMPI Alexithymia Scale (MMPI-A) obtained by selecting a number of items related with BIQ scores from the Minnesota Multiphasic Personality Inventory. In the mid-80s, Krystal et al. (11) developed the Alexithymia Provoked Response Questionnaire (APRO) which was derived from a particular version of the BIQ. These questionnaires did not take into consideration the psychometric standard of test construction and provided only minimal empirical support for the construct of alexithymia.

A psychometrically sound measure of alexithymia started to be developed at the University of Toronto by the "Toronto group" in the mid-80s under the name of Toronto Alexithymia Scale [TAS; (12)]. This attained its final form as a self-report scale consisting of 20-items (TAS-20) about a decade later (13). Its validity has been tested in conjunction with other personality constructs and through several translation in other languages [cf. e.g., (14)]. TAS-20 also has the advantage of being brief and easy to administer. For these reasons, it is the most widely used measure for the assessment of alexithymia. This does not mean that the TAS-20 is the only psychometrically valid tool currently used for the assessment of alexithymia. Indeed, at least one alternative instrument must be mentioned, e.g., the Bermond-Vorst Alexithymia Questionnaire (BVAQ), a self-report measure which generally corresponds quite closely to dimensions of the TAS-20 (15).

The development of a standardized instrument allowed researchers to study alexithymia in relation to various clinical and non-clinical phenomena. This has made it possible to substantiate the observation that alexithymia is related with psychosomatic diseases. Moreover, alexithymic characteristics were found in various clinical conditions characterized by a disordered affect regulation (5), such as depression (16), self-harm and suicidality (17–19), schizophrenia (20), eating disorders (21, 22), substance use disorder (23) and autism spectrum disorder (24, 25). Hence, alexithymia started to be considered a non-specific vulnerability factor involved in the development of physical and mental disorders as well as a specifier associated with adverse outcomes when treating such conditions [see e.g., (26, 27)]. Concurrently, alexithymia was associated with several medical conditions such as diabetes, cancer or chronic illnesses (28–30).

Today, alexithymia is regarded as a personality trait and as a "sub-clinical phenomenon" (31) and it was never included in the Diagnostic and Statistical Manual of Mental Disorders (DSM), although it is recognized as one of the main clusters within the Diagnostic Criteria of Psychosomatic Research (32, 33). From a non-clinical perspective, the construct of alexithymia has drawn the attention of people interested in exploring wider psychological issues concerning emotional competence (34), emotional intelligence (35, 36) as well as related questions regarding empathy and theory of mind [cf. e.g., (37–41)].

As this introduction briefly illustrates, the history of the alexithymia construct is quite complex. Even though this is originally defined in a restricted domain, in time it has become more transversal and relevant for the study of a wide range of phenomena. In fact, today alexithymia appears to be essential to understand–among other things–how emotions and emotion regulation work. For this reason, the literature counts a dozen books and more than 5,000 scientific publications on alexithymia, retrievable from the main bibliographic databases (i.e., Web of Science, Scopus, Google Scholar, PsycInfo, PubMed). Many attempts have been made to analyze this literature in order to identify how the debate on this construct is articulated. According to the Web of Science database, there are more than 200 reviews issued on this topic from the beginning of the discussion on alexithymia till now. Some of these played a significant role in the development of this concept. Considering only the most recent times (from 2005 to 2020), 50 systematic reviews based on meta-analytical methods were published. These papers usually focus on specific aspects of alexithymia (i.e., on

its relation with eating disorders, risky drinking, suicide, etc.) and they are often aimed at disambiguating the divergence in empirical results of single studies.

Despite previous literature providing a widespread overview of specific theoretical and empirical aspects of alexithymia, to our knowledge none of these works make use of a quantitative approach to investigate the complex and transversal character of this construct in its evolution and multiple ramifications. In fact, different from previous meta-analyses focusing on individual aspects of alexithymia, our study aims at approaching alexithymia research as a whole and analyzes how the scientific production on this condition is organized. Among other things, we would like to identify distinct areas in alexithymia research and explore how they change with time. We also aim to investigate which topics of interests are in the various development stages of the construct and which methods and techniques have been used to address alexithymia. In this way, we aim to reconstruct the same organic image of alexithymia research previously portrayed in theoretical and historical literature reviews, but through a bottom-up approach borrowed from Scientometrics.

Scientometrics applies quantitative methods to measure and shape the development of science, seen as an informational process (42). Some of the main themes in Scientometrics include ways of measuring research quality and impact, understanding the processes of citations, and mapping scientific fields and the use of indicators in research policy and management (43). For our purposes, Scientometrics can help us to deal with the difficulties arising from the exponential growth of the literature on alexithymia in the last few decades by providing a means to organize it in meaningful structures [for a review of the utility of Scientometrics for this purpose, see e.g., (44, 45)].

The bottom-up approach used in scientometric reviews has already been proved successful to assess trends and the evolution of assessment instruments or techniques developed in narrow disciplinary domains such as linguistics and psychology (46, 47).

In the present study, (i) a corpus of scientific documents is identified via the Web of Science (WoS) search algorithms; (ii) the identified articles and their references are segmented and classified by co-citation techniques developed by CiteSpace software (48–50); and (iii) they are analyzed in their content, according to the prominent trends identified by the CiteSpace software.

Within Citespace, cited papers are represented by interactive maps across the domain of space and time to obtain a depiction of almost 50 years of research in alexithymia across the world. The algorithms developed to measure the strength of links between citing and cited publications are able to create clusters of papers or journals focusing on thematically distinct aspects of alexithymia. In addition, reliable parameters implemented in the software can estimate the impact of publications or editorial venues on their specific cluster and on the overall corpus of documents retrieved on the topic. This allows us to identify the most influential publications on alexithymia and the most pursued issues considered by the research in relation to different time frames. Moreover, we can pinpoint the shifts in the research lines on this subject as well as of the approaches employed to investigate this condition.

To summarize, this study examines the extent to which the historical reconstructions of alexithymia research suggested in traditional narrative reviews are replicable using a bottom-up scientometric approach based on knowledge mapping techniques.

MATERIALS AND METHODS

Data Source and Descriptive Statistic

The data used for the analyses include 4,930 publications on the conceptual analysis, assessment and neurophysiological correlates of Alexithymia published between January 1st 1980 and May 1st 2020, with 100,251 references downloaded from the WoS Core Collection. The reason for using WoS is due to its coverage of published research on alexithymia, which is higher than alternative databases such as Scopus, Pubmed or EBSCO. The search syntax adopted for this study was Topic ("Alexithymia") OR Topic ("Alexithymic"). By means of the search field Topic, WoS extracts title, abstract, and keywords. From an initial pool of 5,390 documents, we excluded those that were written in languages other than English, thus arriving at a final sample of 4,930 publications with their 100,251 references (see **Figure 1**).

Supplementary Figure 1 reports the number of documents by year. Overall, it can be observed that there was an exponential growth in the research on Alexithymia from its start till the present day. The WoS database contains <10 publications per year dating from the early 80s; these reached a median of $\sim$100 publications per year for the first time in the year 2002 and then a median of 200 in 2010. They joined their highest point in 2019 with more than 400 publications, which alone corresponded to 9% of the overall production on alexithymia stored in the WoS database.

Supplementary Table 1 presents the results of frequency analysis performed on the sample of 4,930 publications which revealed document typologies and the most productive authors, universities/institutes, and countries/regions. Considering the document typologies defined by WoS, most of the documents fell under the category "Articles" (78%), which was followed by the category "meeting abstract" (13%), "review" (3.7%) and other few categories with lower incidence. Among the most prolific authors, there were the three authors (G. J. Taylor, R. M Bagby and J. D. A Parker) of the Toronto Alexithymia Scale (TAS-20), respectively, at first, second and fourth position (with 91, 83, and 62 publications). Other prolific authors were O. Luminet (70 publications), Fukunishi (56 publications), and M. Youkamaa (55 publications). As for the most prolific organizations, the University of Toronto topped the list with 148 publications, followed by the University of London with 99 publications and the University of Rome "La Sapienza" with 95 publications. Among the most prolific countries, USA topped the list with 1,155 publications, contributing 23% of the overall production. It followed Italy (16%), England (9%), and Canada (8%). The first two Asian countries were Turkey (3.5%) and Japan (3.2%), respectively, at the 11th and 12th position.

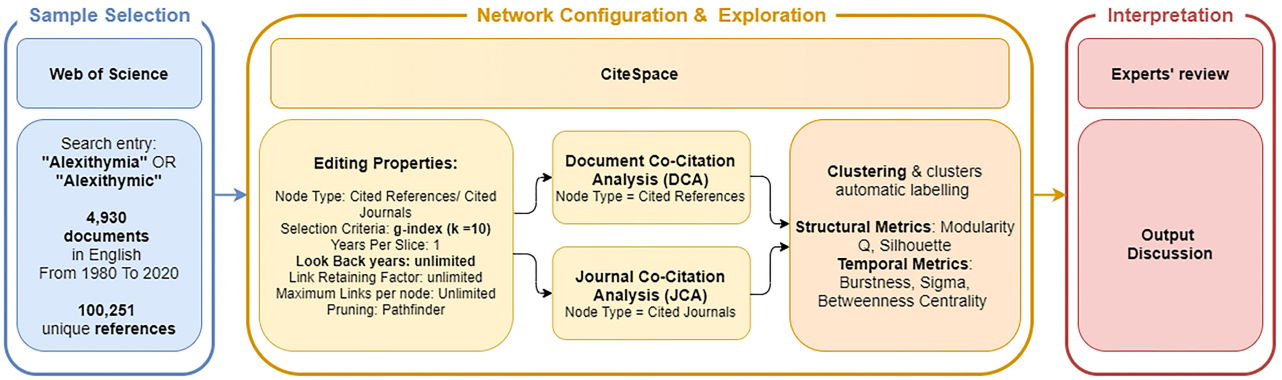

FIGURE 1 | Overview of the study protocol.

Data Analysis and Visualization With CiteSpace

The data were exported from the WoS, producing text files containing the "full record and cited references" for each of the 4,930 publications retrieved. CiteSpace software, Version 5.6.R5 (48–50), was employed in order to analyze the data. Document co-citation analyses (DCA), which represents the number of times two publications were co-cited (cited together) in later publications, was employed to individuate time-evolution of the most influential publications and the most pursued themes and techniques, while journal co-citation analysis (JCA), which represents the number of times two journals were co-cited (cited jointly) in publications, was adopted to differentiate the time evolution of disciplinary domains. It should be noted that a small amount of references (0.3%) could not be processed by the software during co-citation analyses. We consider this percentage as a negligible loss of data (51).

CiteSpace was used to generate and analyze two types of networks of co-cited references via DCA and JCA. The DCA and JCA networks were computed separately, using the same criteria described below. The time span of the two networks ranged from 1980 to 2020, with the time slicing configuration at 1 per year. We compared three criteria for node selection to identify the optimal DCA and JCA networks: Top N, Top N%, and g-index. Top N function picks up the N most cited articles and uses information from them to form the network for each time slice. Similarly, Top N% includes the Top N% most cited articles in each time slice to construct the network. G-index criterion (52) represents a variant of h-index, which considers the number of citations of an author's most important publications. Specifically, the g-index is the "largest number that equals the average number of citations of the most highly cited g publications" (51). The networks built with Top N with N at 50, Top N% with N at 10, and g-index with a scaling factor at 10 and 25 were compared. Eventually, we selected g-index criterion with a k scaling factor of 10 because it displayed greater silhouette and modularity indexes and a major consistency in cluster structure. Moreover, the cluster configuration could be better replicated using different versions of the software. In the construction of the network, we edited properties in a way to be as comprehensive as possible. Therefore, the "Look back years" parameter was set at −1, indicating that all the references cited in a citing paper were considered to construct the network, independently from their temporal distance from the source paper. At the same time, we set the "Link Retaining Factor" and the "Maximum Links per node" parameters as unlimited, thus allowing the program to explore all the links between cited publications. After a first visualization of the network, we decided to apply the Pathfinder function. This function consists of a link reduction algorithm (53), which gave us a more predictable and interpretable network configuration.

Metrics of Interest

Modularity Q index and average silhouette metrics were considered to detect the overall structure of the networks, while burstness, betweenness and sigma metrics were considered to assess how the structural and temporal properties of single nodes (publications, journals) impact the networks.

Modularity Q Index

A network's modularity is a global measure of the overall structure of the network (54, 55), which measures the extent to which a network can be decomposed into multiple components, or modules. The modularity Q index ranges from 0 to 1, where, as a rule of thumb, a value close to 1 means that the network is clearly divided into distinct groups.

Silhouette

The silhouette value of a cluster measures the quality of a clustering configuration. Its value ranges between −1 and 1, where values over 0 indicate major homogeneity (50). A silhouette value can be computed for the overall network or for the inner clusters. It might be considered that small clusters usually present a stronger silhouette due to the higher homogeneity of small samples.

Burstness

Citation burstness measures the burst of citations to a given node. CiteSpace explores the bursts of nodes within a given network through Kleinberg's algorithm (56). Burstness index can

be detected for single nodes (references, journals etc.) or for entire clusters. If a cluster contains numerous nodes with strong citation bursts, then, the cluster as a whole captures an active area of research or an emerging trend.

Betweenness Centrality

Betweenness centrality (57, 58) measures the extent to which paths in the network go through a certain node. In CiteSpace, betweenness centrality scores are normalized to the unit interval [0, 1]. A node of high betweenness centrality is usually one that connects two or more large groups of nodes with the node itself as the in-between, hence the term betweenness. A node with a strong betweenness centrality score represents a paper or a journal with great influence inside the network. CiteSpace highlights nodes with high betweenness centrality with purple trims. The thickness of a purple betweenness centrality trim is proportionate to the strength of its betweenness centrality.

Sigma ($\sum$)

A composite metric sigma is defined in CiteSpace to measure the combined strength of structural and temporal properties of a node, namely, its betweenness centrality and citation burst. Sigma is computed as $(\text{centrality} + 1)^{\text{burstness}}$ (50), with higher values indicating works with higher influential potential.

Cluster Visualization and Labeling

The clustering function in CiteSpace has been used to find the major entities in which single nodes could be grouped inside the network. Clusters are numbered depending on their size, starting with the largest (#0) to the smallest (#5). In CiteSpace, version 5.6.R5, three functions are available to label clusters: Log-Likelihood Ratio (LLR), Latent Semantic Indexing (LSI) and Mutual Information (MI). The three methods have been applied to the current DCA networks. We implemented the LLR function, given the higher informative content associated with the output labels. This approach is supported by the same software creator, who pointed out the best performance of LLR in terms of "uniqueness and coverage" of labels (59). Therefore, we used two visualization methods to analyze our networks: the cluster view and the timeline view. The cluster view (**Figure 2**) produces a spatial representation of the network shaped over time, where the layout of clusters inside the network reflects the connections between their nodes. The size of the circles reflects the amount of cited references inside the clusters. The colored shades indicate the passage of the time, from past (purplish) to the present time (reddish)–that is, from cold colors to warm colors. For instance, since Cluster #1 has many bluish and purple edges and nodes, we can infer that it is the oldest cluster among all. On the other hand, colored tree rings refer to the nodes with high betweenness centrality (purple tree rings) and burstness (red tree rings). In the timeline view (**Figure 3**), major clusters are horizontally arranged. The earliest nodes are placed at the leftmost position, whereas the most recent ones are placed at the rightmost positions. Vertical links between nodes indicate citation links between publications belonging to different clusters.

RESULTS

Document Co-citation Analysis (DCA)

The document co-citation analysis produced a network with modularity Q index and average silhouette metric of 0.51 and 0.75, respectively, suggesting moderate modularity and high homogeneity (**Figures 1**, **2**).

Table 1 shows the six major research clusters detected using the clustering function and labeled using the LLR function. Clusters were numbered in descending order based on the cluster size, starting from the largest cluster #0 ("Personality Disorder" size = 185; silhouette = 0.64; mean year = 2002), to the smallest #5 ("Psychological factor"; size = 27; silhouette = 0.93; mean year = 1997). With regard to the time span covered by clusters, it should be noted that overall, all clusters were very extensive in the time domain. Indeed, cluster duration ranged from 39 to 60 years, thus presenting frequent overlaps in time. This result was consistent with the edit properties selected, with the "Look back year" parameter set as unlimited. Nevertheless, it was still possible to distinguish cluster timelines on the basis of the mean year for each cluster and the visualization of major bursts within each cluster (see **Figures 2**, **3**). For instance, cluster #1 ("MMPI alexithymia scale") was the oldest one (mean year = 1978), as understandable also by its purplish color (**Figure 2**). On the contrary, cluster #4 ("Autism spectrum disorder") represented the most recent one (mean year = 2005), as understandable by its light yellowish color in **Figure 2**. Relying on the timeline visualization (**Figure 3**) and on the mean years, we could distinguish clusters #2 and #3, both titled "Toronto Alexithymia Scale" by the Log-Likelihood Ratio (LLR) function. Within CiteSpace, cluster labels are chosen with reference to the title terms, keywords, and abstract terms of citing documents (49). Therefore, the term "Toronto Alexithymia Scale" could have been mentioned by several influential citing publications in these two clusters, and thus it was chosen by the LLR function. However, cluster #2 (mean year = 1990) is chronologically anterior to cluster#3 (mean year = 2002). Concerning the biggest cluster #0 ("Personality Disorder"), we noticed a sustained activity with bursts occurring at spots distant in time (see **Figure 3**). This result suggests a higher heterogeneity within this cluster, as confirmed by the moderately low silhouette value (= 0.64) and by the analysis of its most representative documents (see the section Discussion).

To understand what the most active areas in the network are, the document bursts have been computed via document co-citation analysis. Among the initial pool of publications and their references, citation bursts sustained for at least 2 years were found for 407 references. In addition, in order to detect which documents had a strategic role in connecting more clusters, we computed betweenness centrality, while publications with potential scientific novelty were explored through the metric sigma.

Table 2 shows the top 25 documents in terms of burst strength, with repetition to the time span of each citation burst (for a complete list, please see **Supplementary Table 2**). Among these, 10 publications belonged to Taylor GY, Bagby RM, and Parker JDA, the group of researchers known for having

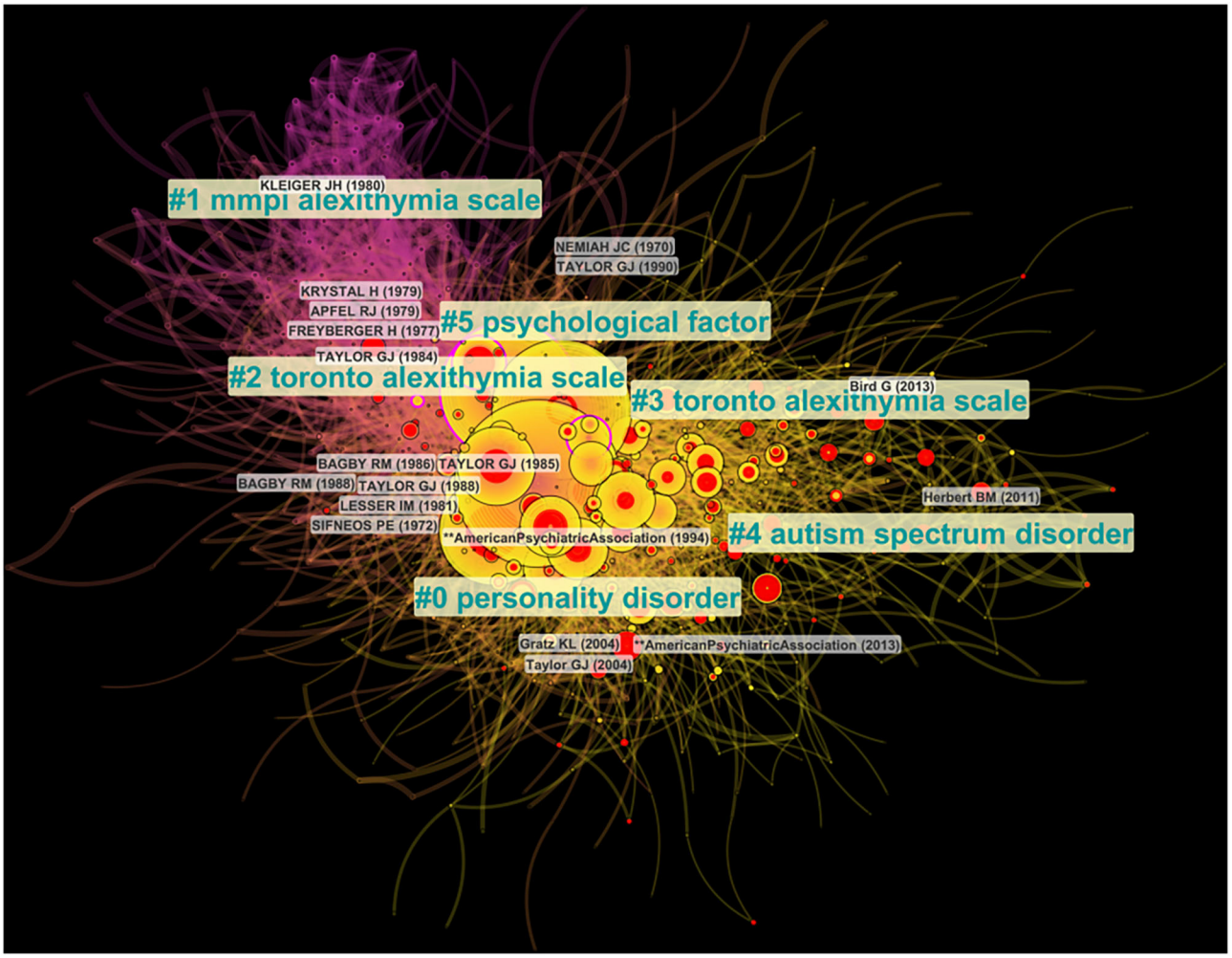

FIGURE 2 | Cluster view of the document co-citation analysis (DCA) generated using CiteSpace Version 5.6.R5 (48–50). Modularity $Q = 0.51$; average silhouette = 0.75. Colored shades indicate the passage of the time, from past (purplish) to the present time (reddish). Colored tree rings refer to the nodes with high betweenness centrality (purple tree rings) and burstness (red tree rings).

developed the Toronto Alexithymia Scale (TAS). The publication attesting to the development of the original TAS (12) was in the first position for burst strength (=70.11). Within **Table 2**, many were early publications playing a crucial function for a conceptual definition of alexithymia (1, 8, 10, 67, 68, 72, 78). Consequently, these were also the publications with the earliest burst beginnings (between 1981 and 1985) and the longest burst duration (lasting between 15 and 21 years). Conversely, the most recent publications within the list (24, 71, 75) presented the shortest burst duration (between 3 and 5 years). However, for these papers, the increasing trend in citation (the burst) was also found in 2020, suggesting that their burst strength and, therefore, their influence is likely to continue for the foreseeable future. Among the other documents appearing in **Table 2**, there were also two different versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, DSM-V), suggesting alexithymia has widely been explored in conjunction with other clinical conditions. Then, we noted that among the documents with highest burst, there were the two influential books by Taylor et al. (5) and Krystal and Krystal (76).

Analyzing the documents with highest sigma values (see **Supplementary Table 3**), we could notice that documents at the top of the list enormously outpaced all the others. This is consistent with the measurement and the conceptualization of sigma as an index of scientific novelty and with case studies by Chen et al. (79) showing that highest sigma values were usually associated with Nobel Prize and other award-winning researchers. On the other hand, overall the publications within our network had a low betweenness centrality index ranging from 0.01 to 0.14 (see **Supplementary Table 3**). The highest centrality score (=0.14) belonged to Sifneos (2) who introduced the term "alexithymia" for the first time, while the highest sigma value (=693.31) belonged to the review of the state of the art research in alexithymia by Taylor (60). The influence of this last publication is also attested by the fact that this was the second record for burst strength and the third record for betweenness centrality

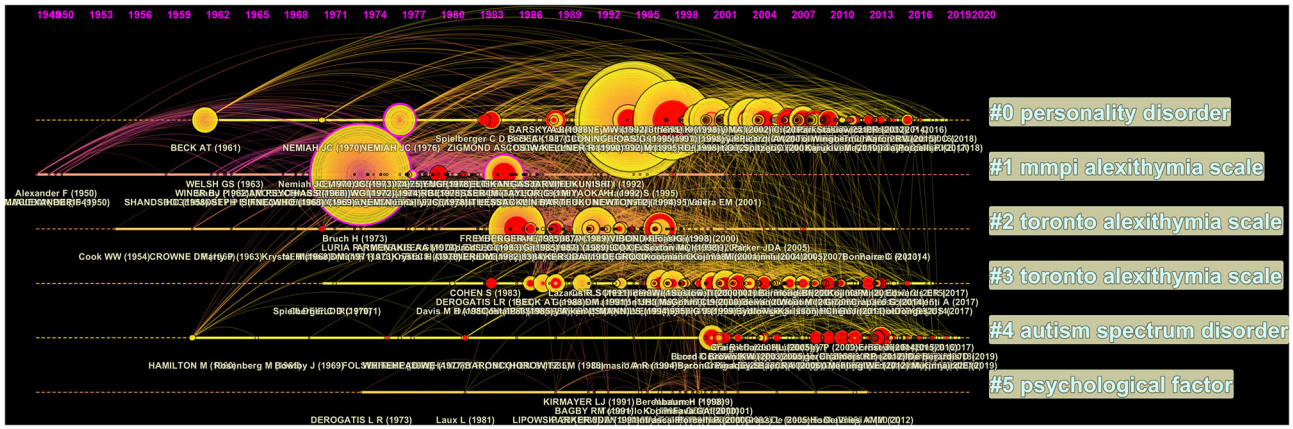

FIGURE 3 | Timeline view of the document co-citation analysis (DCA) generated using CiteSpace Version 5.6.R5 (48–50). Modularity Q = 0.51; average silhouette = 0.75.

TABLE 1 | Clusters computed via Document co-citation Analysis (DCA).

Cluster ID	Cluster label	Size	Silhouette	Mean (year)	From	To	Duration of the cluster (in years)
0	Personality Disorder	185	0.64	2002	1961	2018	57
1	MMPI alexithymia scale	147	0.86	1978	1948	2001	53
2	Toronto alexithymia scale	147	0.62	1990	1954	2014	60
3	Toronto alexithymia scale	140	0.71	2002	1970	2017	47
4	Autism spectrum disorder	73	0.82	2005	1960	2019	59
5	Psychological factor	27	0.93	1997	1973	2012	39

Cluster labels are obtained via the LLR method. Cluster IDs are in decreasing order depending on cluster size. Size equals the number of cited documents within the cluster. Cluster duration in years depends on the time span from the oldest to the most recent paper. Silhouette is an index of cluster homogeneity, with values approaching 1 indicating the maximum in homogeneity.

(0.11). Other influential documents were the paper presenting the TAS (12), first for burst strength and second for sigma value (=151.25), and the paper where Freyberger (68) introduced the concept of "secondary alexithymia," which is attested third for sigma (=76.13) and second for centrality score (=0.13).

Journal Co-citation Analysis (JCA)

The JCA produced a network with a total modularity Q score at 0.47 and an average silhouette score of 0.74, indicating moderate modularity and high homogeneity. JCA represents an aggregation at a higher level than DCA, since articles published in the same journal are lumped together to form a supernode in a network of journals. Inside the JCA network, 332 nodes (journals) had a burst history of at least 2 years.

Table 3 shows sample journal bursts computed via Journal Co-citation Analysis (JCA). It should be noted that CiteSpace was not able to capture the difference between book titles and journals automatically. Therefore, in displaying results (**Table 3**) we selected only journals (for a complete list, please see **Supplementary Table 4**).

The journals in the first two positions for burst strength were, respectively, *Psychotherapy and Psychosomatics* (strength = 164.51) and "Psychosomatic Medicine." These journals stand out also for the longest duration of their citation burst, estimated at 26 years. The citation burst for these journals dated back to 1980, but it could be more distant in reality, considering the time limitation of the WoS database, which collected documents starting from 1980. Other journals whose citation burst started in the early '80s report all in their titles the terms "psychosomatics" and "psychotherapy" (*Modern Trends Psychotherapy, American Journal of Psychotherapy, Short Term Psychotherapy, and Modern Trends in Psychosomatic Medicine*). From DCA, we observed that the papers with the highest citation burst, centrality and sigma (**Table 2**) published during the '70s fell within the aforementioned journals [see (57, 58, 59, 8, 60]. Additionally, the journals within the psychiatric discipline presented a long duration in citation burst (between 13 and 23 years). Among these, the *American Journal of Psychiatry* stands out as the most influential one (third for burst strength = 125.12). Other journals within the psychiatric discipline were the *Journal of Nervous Mental Disorders*, the *British Journal of Psychiatry*, *Psychiatric Clinics of North America* and the *General Hospital Psychiatry*. Influential journals with still active citation bursts were *Frontiers in Psychology* and *Plos One*, which were fourth and fifth ranked for burst strength respectively, despite the limited burst duration (4-5 years). Lower in the list, there were *Frontiers in Psychiatry*,

TABLE 2 | List of the top 25 documents for burst strength, estimated via document co-citation analysis (DCA).

References	Publication title	Burst strength	Burst begin	Burst end	Centrality	Sigma	Cluster ID
Taylor et al. (12)	Toward the development of a new self-report alexithymia scale.	70.11	1988	2003	0.07	151.25	2
Taylor (60)	Alexithymia: concept, measurement, and implications for treatment.	64.39	1985	2003	0.11	692.91	1
American Psychiatric Association (61)	American Psychiatric Association. DSM-V	58.38	2015	2020	0.01	1.71	4
Apfel and Sifneos (8)	Alexithymia: Concept and measurement.	57.74	1981	2001	0.07	38.48	1
Taylor et al. (62)	Criterion validity of the Toronto Alexithymia Scale.	54.25	1989	1998	0.03	5.94	2
Bagby et al. (63)	Toronto Alexithymia Scale: Relationship with personality and psychopathology measures.	49.15	1988	2002	0.03	3.41	2
American Psychiatric Association (64)	American Psychiatric Association. DSM-IV	39.53	1998	2012	0.05	6.89	0
Bagby et al. (65)	Alexithymia: a comparative study of three self-report measures.	38.07	1988	2001	0.01	1.43	2
Gratz and Roemer (66)	Multidimensional assessment of emotion regulation and dysregulation	37.43	2016	2020	0.03	2.58	3
Krystal (67)	Alexithymia and psychotherapy	37.35	1981	2001	0.06	7.81	1
Kleiger and Kinsman (10)	The development of an MMPI alexithymia scale.	36.89	1981	1998	0.04	3.98	1
Freyberger (68)	Supportive psychotherapeutic techniques in primary and secondary alexithymia.	36.20	1982	2003	0.13	76.13	1
Lesser (1)	A review of the alexithymia concept.	35.79	1983	1998	0.05	4.89	1
Sifneos (2)	Short-term psychotherapy and emotional crisis.	33.68	1981	2001	0.06	7.53	1
Taylor et al. (69)	Validation of the alexithymia construct: A measurement-based approach.	33.59	1992	2000	0.01	1.24	2
Taylor and Bagby (70)	New trends in alexithymia research.	32.31	2006	2012	0.04	3.56	0
Herbert et al. (71)	On the relationship between interoceptive awareness and alexithymia.	31.90	2015	2020	0.01	1.22	4
Bird and Cook (24)	Mixed emotions: the contribution of alexithymia to the emotional symptoms of autism.	31.90	2015	2020	0.02	1.93	4
Nemiah and Sifneos (72)	Affect and fantasy in patients with psychosomatic disorders	31.54	1985	2006	0.04	3.77	2
Parker et al. (73)	Factorial validity of the 20-item Toronto Alexithymia Scale.	30.40	1995	2006	0.03	2.23	2
Taylor et al. (5)	Disorders of Affect Regulation. Alexithymia in Medical and Psychiatric Illness.	29.98	1998	2010	0.03	2.57	0
Taylor et al. (74)	Alexithymia and somatic complaints in psychiatric out-patients.	29.47	1994	2002	0.03	2.15	2
Bird et al. (75)	Empathic brain responses in insula are modulated by levels of alexithymia but not autism.	28.67	2013	2020	0.01	1.53	4
Krystal and Krystal (76)	Integration and Self-Healing: Affect, trauma and alexithymia	28.27	1989	2001	0.03	2.48	2
Blanchard et al. (77)	Psychometric properties of a scale to measure alexithymia.	27.82	1982	1992	0.02	1.68	1

For each document are reported burst begin and end, betweenness centrality, sigma and the Cluster ID to which they belong.

Social Cognitive and Affective Neuroscience, *Scientific Reports—UK*, *Frontiers in Human Neuroscience*, and *Neuroscience & Biobehavioral Reviews*, all active between 2015 and 2020.

DISCUSSION

Major Thematic Clusters Found via DCA

The content of major clusters obtained via document co-citation analysis (DCA) is discussed below. Cluster presentation follows a chronological order (for a list of the main citing and cited publications subdivided by cluster ID, please see also **Supplementary Tables 5, 6**).

Cluster #1: "MMPI Alexithymia Scale"

Cluster #1 is the oldest and it contains some of the major papers written between the '70s and the early '80s, which significantly contributed to the definition of the construct and to research on its etiology. The title of the cluster ("MMPI Alexithymia Scale") refers to one of the original assessment instruments, developed by Kleiger and Kinsman (10). This is due to the fact that many influential citing documents within cluster #1 refer to the MMPI Alexithymia Scale in their title, abstract or keywords (see **Supplementary Table 5**). Although this title is not representative of the topic of the cluster, it captures the fact that the most influential papers date back to a period preceding the development of TAS. Indeed, major bursts refer to studies which presented or validated the first instruments to measure the construct of alexithymia: the Beth Israel Hospital Psychosomatic Questionnaire (2), the Schalling-Sifneos Personality Scale (8), and the already mentioned 22-item MMPI Alexithymia Scale (10). Among the other influential publications included in this cluster, there are the seminal publications by Sifneos on the construct of "alexithymia" (2, 78). A pivotal role is also played by Freyberger's (68) paper, introducing the concept of "secondary

TABLE 3 | List of the top journals for burst strength, estimated via Journal Co-citation Analysis (JCA).

Journal	Strength	Begin	End	Duration
Psychotherapy and Psychosomatics	164.51	1980	2006	26
Psychosomatic Medicine	138.78	1980	2006	26
American Journal of Psychiatry	125.12	1985	2006	21
Frontiers in Psychology	88.00	2016	2020	4
Plos One	74.82	2015	2020	5
Modern Trends in Psychosomatic Medicine	73.19	1980	2001	21
Journal of Nervous Mental Disease	65.90	1981	2004	23
American Journal of Psychotherapy	58.20	1981	2002	21
Psychosomatics	56.71	1992	2005	13
Short Term Psychotherapy	51.76	1981	2001	20
British Journal of Psychiatry	47.05	1993	2006	13
Psychiatric Clinics of North America	46.64	1988	2001	13
Psychological Reports	46.48	1995	2007	12
British Journal of Medical Psychology	40.12	1990	2007	17
New England Journal of Medicine	35.91	1985	2008	23
General Hospital Psychiatry	35.26	1981	2001	20
Int J Psychoanalytic Psychotherapy	34.19	1984	2004	20
European Journal of Personality	33.69	1995	2008	13
New Trends Exp. Clin. Psychiat	31.10	1995	2003	8
Frontiers in Psychiatry	31.05	2017	2020	3
Soc Cogn Affect Neur	29.04	2014	2020	6
Scientific Reports-Uk	29.03	2017	2020	3
Journal of Human Stress	28.82	1986	2004	18
Frontiers in Human Neuroscience	27.74	2015	2020	5
Neuroscience & Biobehavioral Reviews	27.12	2016	2020	4

alexithymia": i.e., a condition acquired in the adulthood as a consequence of an organic disease, a chronic illness or an invasive medical treatment (i.e., dialysis, transplant). The contribution of Krystal in defining the etiology of the construct is evident in two prominent publications on patients with substance abuse behaviors and clinical cases of post-traumatic stress disorder (PTSD) (67, 80). The paper with the highest burst strength and sigma value within the cluster and the overall network is a review by Taylor (60), which summarizes the knowledge on alexithymia collected until that time, illustrating the medical and psychiatric disorders that are usually associated with it as well as the diagnostic instruments developed so-far and the difficulties to treat, with psychotherapy, people suffering from alexithymia. This publication probably represented a turning-point since it provided a systematic framework for the theoretical foundations of the construct and, at the same time, it highlighted the limitations of the knowledge available at that time, preparing the field for the development of a new assessment instrument, presented by Taylor et al. just 1 year later (12).

In brief, Cluster #1 collects the early literature on alexithymia that goes from the '70s to the mid-1980s, a period which is antecedent to the advent of the Toronto Alexithymia Scale and was focused on the theoretical definition of the construct mainly in connection with psychosomatic diseases.

Cluster #2: "Toronto Alexithymia Scale"

The title of this cluster refers to the Toronto Alexithymia Scale [TAS, (12)] and it appears appropriate for this group of articles. The scale discussed by the papers included in this collection is the first version of the TAS. The articles based on the final version of the Toronto Alexithymia Scale (TAS-20) are included in cluster #0, named "Personality Disorder." Therefore, this cluster represents the first stage of the research program fostered by the researchers of the University of Toronto, which aimed to evaluate the validity of the construct of alexithymia "using a measurement-based, construct validation approach" (69). Within this cluster, major bursts are all represented by papers written by one or more exponents from the group of Toronto. Two are the exceptions to this intellectual monopoly. A first one is represented by Krystal's book (76) which provides an overview on the link among alexithymia, emotional regulation and traumatic experiences and which drives the attention of the research on an aspect of alexithymia which was mostly neglected, i.e., its relationship with anhedonia. Indeed, people who suffer from an altered emotion awareness also exhibit an altered sensibility of the hedonic tones of their experience, especially of the positive ones. The second exception is surprisingly represented by an earlier publication by Nemiah and Sifneos (72), which presented excerpts of clinical interviews with patients suffering from psychosomatic disorders as well as some notes by the authors on them. The patients' reports included in this article describe the characteristics that 3 years later will be considered as crucial to qualify the alexithymic condition. The relevance of this paper became clear only after the work of the Toronto Group and their efforts to identify the main factors characterizing the construct of alexithymia, as witnessed by the late burst beginning, dating back to 1985 (see **Table 2**). All other prominent publications within the cluster discuss the psychometric properties of the first version of the Toronto Alexithymia Scale: they present its criterion validity (62) or test its construct validity (63) or, again, they compare this instrument with previous ones such as the Schalling-Sifneos and the MMPI-A scales (65). Of prominent relevance is also the subsequent review by Taylor et al. (81), first for centrality (=0.09) within the cluster. By suggesting that alexithymia represents "a potential new paradigm for understanding the influence of emotions and personality in physical illness and health," this paper paves the way for a conceptualization of alexithymia as a non-specific vulnerability factor that can potentially represent a predisposition for the onset of personality disorders and/or of disorders related with emotional dysregulation. Indeed, within the clusters some influential papers focused on the use of TAS to assess alexithymic characteristics in new clinical conditions such as feeding and eating disorders (82–84). Another line of research focuses on the relationship between depressive and anxiety disorders and alexithymia, as measured with TAS (85, 86).

To sum up, the cited publications within cluster #2 cover the period between 1985 and the early '90s. They include studies which are mainly related to the first version of the Toronto Alexithymia Scale. In the clinical contexts, these studies focused primarily on the relationship between alexithymia and eating disorders, anxiety or depression.

Cluster #0: "Personality Disorder"

This cluster, with its 185 cited references, is the largest one. Here, the most influential publications start from 1994, in other words, after the development of the new 20-item Toronto Alexithymia Scale. Notably, the two publications presenting the psychometric properties of the new TAS-20 (13, 87) share an impressively high citation frequency (=1941; =1161), although they have no bursts or very low burst. This phenomenon could be due to the fact that the new scale did not represent a revolutionary change in the way alexithymia was assessed, contrarily from the first TAS, which ranked first position for burst strength and sigma. Therefore, these publications did not experience an abrupt explosion in citations, although they might have been cited by all the following studies employing this new version of TAS. Consequently, they represent the document with the highest number of citations in the overall DCA network. The central role of the "Toronto Group" in this cluster is also evident from other documents in first positions within the cluster for burst and sigma metrics, mainly: the book by Taylor et al. (5) and a subsequent review (88) exploring the relationship between alexithymia and, more generally, emotion regulation/dysregulation for mental and physical health in general; two methodological papers (89, 90) testing the validity and reliability of TAS-20 in different linguistic and cultural contexts; a review by Taylor and Bagby (70), which suggests a shift in research on alexithymia from "measurement-based validation studies to experimental investigations," exploring the relationship between alexithymia and various aspects of emotional processing through the employment of standardized emotional task and the measurement of brain activity and physiological responses (see cluster #3, renamed by us "Emotion Information Processing"); a publication by Bagby et al. (91) presenting the Toronto Structured Interview for Alexithymia (TSIA), to be used together with the self-report TAS-20 to guarantee a multimethod assessment of alexithymia. Although there is certain heterogeneity in the cluster (silhouette = 0.64), influential publications by other authors can be thematically and methodologically connected with the lines of research pursued by the mentioned publications by the Toronto Group. For instance, the link between the ability to regulate emotion and the consequences for physical and mental health is captured in publications by Lumley et al. (92) and Grabe et al. (93). Moreover, few papers review specifically the relationship between alexithymia and depression (94) or alexithymia and alcohol abuse disorders (95). This fact explains why the DSM-IV (64) was the document with the highest citation burst within the cluster. Some publications continue to explore the psychometric properties of TAS in different populations (96) or in conjunction with other phenomena, such as the construct of personality (97) or the theory of the levels of emotional awareness (98). A paper by Ogrodniczuk et al. (99) reviews the challenges and the solutions developed to treat patients with alexithymia through psychotherapy. Finally, in a relatively high position for burst strength, there is a review by Sifneos (100), titled "Alexithymia: Past and Present" which is one of the most recent papers written by Sifneos on alexithymia.

In short, this cluster covers research on alexithymia spanning from the mid-1990s to the late 2000s. This period follows the development of the TAS-20 and it is largely influenced by the research of the Toronto Group. Articles by other groups employ this new self-report instrument to investigate the relationship that alexithymia entertains with a variety of clinical conditions or emerging constructs related to personality and emotional competence.

Cluster #5: "Psychological factor"

This cluster is relatively small, comprising exactly 27 cited papers. The majority of cited publications are contemporary to a number of those included in Cluster #0 ("Personality Disorder") and in Cluster #3 ("Emotion Information Processing"), dating back to the second half of the '90s. Thematically, publications within this cluster address alexithymia as a risk factor for mental and physical health conditions. The relationship between alexithymia and depression is explored in a paper by Honkalampi et al. (101), first for citation burst within the cluster, and in later publications (102, 103), which examine the potential relationship between alexithymia and the regulation of the immune-inflammatory responses. Other works explore the relationship between alexithymia and defense style (104) or neuroticism (105). The influence of alexithymia for physical health is studied in conditions such as functional gastrointestinal disorders (106, 107), inflammatory bowel disease (108) or hypertension (109). More generally, this relationship is highlighted by bursts in publications referring to psychosomatic research (32, 110). Within the cluster, few influential publications still focus on the exploration of the psychometric properties of instruments prior to TAS-20. Among these, one study suggests a revision of TAS (111), while two publications by the Toronto Group question the values of previous instruments such as MMPI-A and SSPS-R (112, 113).

Overall, cluster #5 collects a small number of publications, posterior to the TAS-20, whose primary aim is to explore alexithymia in psychopathology and physical illness.

Cluster #3: "Toronto Alexithymia Scale" (Renamed: "Emotion Information Processing")

The major publications within this cluster chronologically follow the development of TAS and TAS-20, while they precede chronologically the papers included in cluster # 4 ("Autism Spectrum Disorder"). The title automatically extracted by the LLR method does not capture the main topic of the cluster, although it captures the fact that the majority of empirical studies mentioned here employ the TAS-20 in their design. In accordance with Aryadoust et al. (114), highlighting the opportunity to employ cluster counter-labels based on expert evaluations of the content of documents within the cluster, we argue that an analysis of the major bursts suggests that a more appropriate title for this cluster would be "Emotion Information Processing." Indeed, the most cited paper within the cluster is Lane et al. (115): this paper puts forward the hypothesis that alexithymia is not simply a problem of emotion labeling, but it is "associated with impaired verbal and non-verbal recognition of emotion stimuli and that the hallmark of

alexithymia, a difficulty in putting emotion into words, may be a marker of a more general impairment in the capacity for emotion information processing" (115). Consistently with this idea, the most pursued line of research consists in the exploration of deficits in the recognition of facial expressions among individuals with alexithymia (116–119). Other studies in this cluster use a wide range of emotional tasks, testing the processing of emotionally salient pictures (120) or the processing of emotional prosody and semantics (121), or again the ability to match emotional stimuli of different nature (115). Some studies test the relationship between alexithymia and empathy (38, 122), mentalization (37) and emotional intelligence (123). As it is pointed out by meta-analyses and reviews on the neural correlates of alexithymia published after 2010 [cf. (124, 125)], the majority of these studies explore their hypotheses by applying neuroimaging techniques. Central within the cluster are the publications by Lane and Schwartz who at the end of the '80s put forward a cognitive-developmental theory of emotional awareness. They considered emotional awareness as the result of a cognitive processing which undergoes five levels of structural transformation of emotional information. They also brought up a related tool [the Levels of Emotional Awareness Scale–LEAS; cf. (126)] to evaluate the individuals' acquisition of emotional awareness from a developmental and ontogenetic perspective. The LEAS is often used as a "reverse control tool" measure for alexithymia and it is inversely correlated with TAS (115, 127, 128). Moreover, a specific theoretical contribution by Lane, Schwartz et al. to alexithymia research derives from their conceptualization of alexithymia as an emotional equivalent of blindsight (129) and as a form of "affective agnosia" (130, 131).

Further analysis of the documents within this cluster shows that between the '90s and the early 2000s many empirical studies were not interested in the condition of alexithymia *per se* but they used the construct of alexithymia in conjunction with others to investigate how emotions are processed. This hypothesis is supported by the presence of a set of highly cited articles referring to instruments which measure people's emotion processing capacities, mainly the Interpersonal Reactivity Index [IRI, (132)], the Positive and Negative Affect Schedule [PANAS, (133)], and the Difficulties in Emotion Regulation Scale (66). A number of studies focus in particular on emotion regulation, as witnessed by the position held by Gratz and Roemer (66), first document for burst strength within the cluster, and by the presence of other publications exploring the relationship between emotion regulation strategies and alexithymia (121) or well-being (134). Lastly, we might point out that within this cluster lies the paper referring to the Bermond-Vorst Alexithymia Questionnaire [BVAQ, (15)]. This self-report instrument was developed to operationalize the modularist conception of alexithymia put forward by its authors. Indeed, in Bermond and Vorst's view, we should distinguish between two different types of alexithymia. These derive from the disruption of different neural structures which support, respectively, the cognitive and the affective component of our emotional capacities. The BVAQ is currently used in conjunction with TAS in many empirical researches, although the latter is still the most used and reliable tool.

In summary, the research included in cluster #3 reflect the cognitive turn in alexithymia research which started from the mid-1990s. The articles belonging to this cluster employ a variety of cognitive tasks and neuroimaging techniques to explore how people with high alexithymia process emotion information in multiple domains (linguistic, visual etc.). Also the studies that introduce new assessment tools for alexithymia (i.e., the BVAQ) or examine alexithymia in conjunction with parallel constructs (i.e., emotional intelligence, emotion regulation and theory of mind) adopt a cognitive and neuroscientific approach.

Cluster #4: "Autism Spectrum Disorder"

This cluster represents the latest trends in alexithymia research and describes an ongoing line of research. The title "Autism Spectrum Disorder" aptly reflects the main point investigated by this cluster of papers, i.e., the comorbidity between alexithymia and Autism Spectrum Disorder (24). This explains also why the DSM-V and DSM-IV have high citation bursts within the cluster; in fact, they are cited mainly to define the condition of ASD. The same rationale applies for the three publications by Baron-Cohen et al. presenting the revised version of the "Reading the Mind in the Eyes" test (135) and the self-report Autism-Spectrum Quotient scale [AQ, (136)] and the self-report Empathy Quotient [EQ, (137)]. Among the main hypotheses investigated in the most influential articles, at least two are worth mentioning. The first one assumes that emotional impairments in ASD are due to the co-occurrence of alexithymia, rather than being a peculiar feature of ASD itself (24, 31, 75). The second one puts forward the idea that alexithymia and, by extension, poor emotional awareness are associated with deficits in viscerception or interoceptive ability (71, 138). Some influential publications in this cluster provide a definition of the neural structures supporting the interoceptive ability (139, 140) measured mainly through the heartbeat detection task. Other influential studies focus on methodological problems related to the measurement of the interoceptive ability (141) and provide theoretical models and methodological solutions to its study in conjunction with alexithymia (142–144). Finally, few recent publications combine the two hypotheses previously mentioned, suggesting that alexithymia could be conceived as a general deficit in interoception (145) and that the alexithymic traits or, more generally, the affective symptoms of people with ASD could be explained by the interoceptive difficulties they experience (146, 147).

In summary, Cluster #4 collects the most recent trends of research which are centered on the relationship between alexithymia and ASD. More specifically, the studies included in this group suggest that alexithymia plays a role as for the socio-communicative deficits exhibited by people suffering from ASD.

Major Disciplinary Domains Found via JCA

Typically, journals are the point of reference of specific research communities: they do not only focus on particular subjects, but they also share a common perspective on them as well as preferred methods for their investigation. To scrutinize which journals published salient research on alexithymia in which periods is relevant to understand how this construct was

approached by different research communities in different times. Therefore, JCA was applied to identify journals cited together in one paper.

Journal titles reported in **Table 3** revealed something relevant concerning the conceptual history of alexithymia: they showed that the concept originated in the field of psychiatry and that it was relevant especially for psychosomatic research (see the title of journals with the earliest burst begin and the longest burst duration). These fields remained crucial for the research on alexithymia for at least 25 years. Then, these publication venues stopped their citation burst around 2002 and 2008. Indeed, almost none of the journals in the list of the top 30 for burst strength (**Table 3**) had an active burst process between 2008 and 2014, suggesting that this was a period of transition, characterized by a plurality of editorial venues addressing the research on alexithymia. Subsequently, from 2014, we found new journals whose citation burstness was still active in 2020 and it is therefore expected to continue with a consequent increase in burst strength index. Titles of the journals with the most recent citation bursts showed quite clearly that alexithymia has become a subject of interest as a different research area. Aspects related with psychosomatics and psychotherapy—which were dominant in the older studies published on this subject—were not mentioned anymore after 2014, indicating a shift in the research focus of the field. On the other hand, neuroscience was the main disciplinary domain of recent journals with a high burst strength (see *Social Cognitive and Affective Neuroscience, Frontiers in Human Neuroscience, Neuroscience & Biobehavioral Reviews*). This suggests that the neurobiological dimension of alexithymia has piqued the interest of researchers and that the field is actively working toward achieving a multifarious understanding of the condition. Moreover, the burst of journals covering a multitude of topics in the psychological sciences (*Frontiers in Psychology*) or, even, the presence of multidisciplinary journals such as *PLOS ONE* and *Scientific Reports* suggests that alexithymia is no longer a narrow niche subject of study. In fact, in this period the construct of alexithymia has become relevant for personality assessment as well as for research on emotional regulation/dysregulation. This is the reason why alexithymia is the object of growing attention by a wider, interdisciplinary scientific community represented by researchers and clinicians active in fields like psychology, psychiatry, medicine, and neuroscience.

CONCLUSIONS

Any scientific domain–as well as any knowledge domain in general–subtends objective relations between different actors: i.e., institutions, authors, and journals. Network analysis represents an opportunity to computationally analyze and graphically represent the relations that characterize specific domains of knowledge.

Here we addressed the construct of alexithymia using co-citation analysis. Although the visibility of a paper is not a sufficient condition to assess its quality and relevance, it would at least be a necessary condition for gaining authority and for exercising an influence in a field. We applied this method to explore the macroscopic changes that occurred in this first half century of research on alexithymia. Specifically, our approach highlights the major thematic and methodological shifts that occurred within the community interested in alexithymia construct. Document Co-citation Analysis (DCA) and Journal Co-citation Analysis (JCA) suggest that the construct of alexithymia experienced a gradual conceptual and disciplinary shift. The analysis of the clusters shows that the body of research on alexithymia might be divided into three temporarily and logically distinct coarse units.

(1) The first unit includes all the early articles published in the so-called "Pre-TAS era," during which the researchers worked at a definition of the construct. The studies of this phase belong mainly to the area of psychosomatic medicine, psychiatry, and psychoanalytic treatment.
(2) The second unit is centered around the activity of the "Toronto Group." This includes the papers aimed at developing a standardized measurement of the construct and at establishing the differences and the overlaps of the TAS-20 with pre-existing constructs such as those of personality, depression etc.
(3) The third unit comprises the studies of the "Post-TAS" era; their goal is to investigate the construct of alexithymia from the point of view of cognitive science and cognitive neuroscience as well as with behavioral and neurophysiological methods.

The multifactorial definition of alexithymia construct proposed by the Toronto Group has established a watershed within the history of alexithymia. The development of a standardized and easy to use tool such as the self-reported TAS-20 has been a driving force for empirical research, especially in the cognitive and neuroscientific domain. This shift in disciplines co-occurred with a modification in the conceptualization of the construct. Specifically, the interpersonal dimension of alexithymia, from peripheral and collateral aspects of the construct, has become the main focus of research. Indeed, the corpus of early publications is represented by cluster #1, which is focused on the recognition of one's own subjective feelings and therefore on the success of insight-oriented psychoanalytical treatment. In contrast, the research post TAS-20, represented by publications inside cluster #3 (renamed by us "Emotion Information Processing) and #4 ("Autism Spectrum Disorder"), focuses on the recognition of external emotional stimuli. This is evident based on the many studies in clusters #3 studying the deficits of individuals with high alexithymia to recognize emotional facial expressions or emotional images. This shift becomes even more evident in cluster #4, where the condition of alexithymia is primarily associated with a deficit in empathy and theory of mind in people with Autism Spectrum Disorder.

This change in intellectual thought concerning the conceptualization of alexithymia has been fostered by the new psychometric tools and by the experimental designs applied in the field of cognitive science. First, the TAS-20 implicitly modified the conceptualization of the construct by considering only three of the original four facets of the construct. Indeed,

the TAS-20 measures (i) the difficulty identifying feelings, (ii) the difficulty describing feelings, and (iii) the externally-oriented thinking, while (iv) impoverished fantasy life has been excluded for psychometric reasons. Secondly, the development of the Toronto Alexithymia Scale gave new impetus to the research on tools to assess alexithymia. Independently from their supportive or skeptical attitude toward the TAS-20, a number of researchers explored the potentialities and the limits of this scale, comparing it with instruments measuring related constructs such as depression, anxiety, personality or emotional intelligence. The availability of a highly standardized and easy to administer instrument to assess alexithymia allowed researchers to explore this condition in various experimental settings by the use of behavioral and neurophysiological techniques. Consequently, this line of research is not any more restricted to the field of psychodynamics and psychosomatics, but has been expanding to a much larger community. Indeed, cognitive science and neuroscience are becoming increasingly pivotal in the field. The more influential publications in cluster #3 and #4 testify to this trend: most of them employ neuroimaging techniques and other neurophysiological measures and address issues concerning the neural basis of emotional processing. The same trend is confirmed by Journal Co-citation Analysis, and in particular by the journals with the strongest recent citation bursts (e.g., *Social Cognitive & Affective Neuroscience, Frontiers in Human Neuroscience, Neuroscience & Biobehavioral Reviews*). The evolution in time of the publications on alexithymia confirms a prediction made by Taylor and Bagby (70) at the end of their review of the "New trends in Alexithymia" at that time: "During the past 10 years alexithymia research has advanced and broadened considerably to include a wide spectrum of methodologies and experimental techniques that offer a significant challenge to alexithymia researchers. The pace of research will likely gain momentum as a result of current trends and increasing collaboration with investigators in other disciplines. The new methods and techniques must be embraced for the field of research to further increase understanding of the alexithymia construct and its association with physical and mental illness" [(70), p. 75]. Indeed, as Taylor and Bagby called for, new methods and techniques were embraced by the alexithymia research and, as a result, this became an interdisciplinary field intersecting a number of disciplines and issues concerning not only clinical psychology but also cognitive sciences and neurosciences.

Yet, some limitations of this study due to methodological problems should be noted.

First, we excluded from our pool of documents all those written in languages other than English (460 studies over an initial pool of 5,390). The use of WoS generates a linguistic bias for a scientometric study since the majority of the journals indexed in WoS are in English; only a small percentage of journals in other languages are included in this database. By excluding the documents written in languages other than English, we probably amplified this bias. However, the language is not irrelevant for the impact of a study: especially in the last decades, with the exception of particular fields/topics, publications written in languages other than English have mostly only a national audience and become relevant for international research only when they are discussed by other publications in English. It is plausible that publications in languages other than English did not catch the attention of a large scientific community; in this case, they would still be invisible in the networks built using DCA and JCA which, by definition, capture only macroscopic trends in research.

Secondly, the use of WoS as reference database also gives rise to a subtler bias related with the fact that psychoanalytic research–like the research in the field of humanities–is presented primarily in books, book chapters and journals that for the most part are not included in WoS or in other bibliometric databases. This applies especially to the past, but in part it still holds true today. Relying on the results we have achieved through our analysis, it seems that psychoanalysis gave a central contribution to the development of alexithymia only until the early'80s, which corresponds to the early years of the history of the construct. According to our scientometric study, it appears that later in time the psychoanalytic tradition gives up its interest in this construct. This is not the case. For example, McDougall (148–150) put forward relevant hypotheses on the etiology of alexithymia, considering alexithymic people as "disaffected" individuals: in her viewpoint alexithymic traits result from the "manifestation of defensives structures of a psychotic kind." McDougall's perspective put forward an influential hypothesis on the psychogenesis of alexithymia, and yet in our psychometric analysis her name and her work do not appear to be relevant for the literature on alexithymia. The same applies for Bucci who developed an influential view on alexithymia on the basis of her Multiple Code Theory. In the perspective she proposes, human experience—including, in particular, emotional experience—is processed at three different levels of symbolizations and alexithymia is a disorder related with this processing (151, 152). Even though these researches do not stand out in our analysis, explicitly or otherwise, they played de facto a relevant role not only with respect to the improvement of the comprehension of alexithymia but also to making explicit its relevance for the cognitive and neuroscientific research [for a discussion on the importance of these authors cf. e.g., (153, 154)].

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

GG contributed to conceiving the study, created the dataset, conducted the analyses, and contributed to literature review and writing the article. AB contributed to the analyses and revising the paper. SD and LP conceived the study, contributed to the literature review, results interpretation, and writing the article. VA contributed to the study design and revising the article. GE conceived the study, obtained funding, and revised the paper. All authors contributed to the article 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/fpsyt.2020.611489/full#supplementary-material

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BRIEF RESEARCH REPORT
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Affective Variables and Cognitive Performances During Exercise in a Group of Adults With Type 2 Diabetes Mellitus

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Previous research has documented that type 2 diabetes mellitus (T2DM) is associated with cognitive impairment. Psychological variables were repeatedly investigated to understand why T2DM patients are poorly active, despite standards of medical care recommends performing aerobic and resistance exercise regularly and reducing the amount of time spent sitting. This exploratory study aims to investigate how affective variables as thoughts, feelings, and individuals' stage of exercise adoption can modulate low cognitive performances during an experimental procedure based on exercise. The Exercise Thoughts Questionnaire (ETQ), Exercise-Induced Feeling Scale (EFI), and Physical Activity Stage of Change were administered to a sample of 12 T2DM patients. The Bivalent Shape Task (BST) alone (BST), BST with exercise [control exercise recovery (CER) + BST], and BST with metaboreflex [post-exercise muscle ischemia (PEMI) + BST] were used as mental task, and response time to congruent, incongruent, and neutral stimuli was recorded. Concomitant cerebral oxygenation (COX) was evaluated by near-infrared spectroscopy (NIRS). As expected, T2DM patients performed significantly better when the stimulus was presented in congruent trials (followed by neutral and incongruent). In the CER + BST session, T2DM patients showed longer reaction time to incongruent trials than in the PEMI + BST and BST alone sessions. Positive feelings toward exercise seem to modulate cognitive performances in high challenging task only if T2DM patients were conscious to play exercise. These results could provide some insights for health intervention targeting exercise for patients with T2DM in order to enhance cognitive performances.

Keywords: type 2 diabetes mellitus, exercise, cognitive impairment, near-infrared spectroscopy, attentional task

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INTRODUCTION

Diabetes is one of the fastest growing health challenges of the 21st century: the number of adults living with diabetes, estimated currently equal to 463 million, having more than tripled over the past 20 years. Type 2 diabetes mellitus (T2DM) corresponds to the most prevalent type of diabetes in the world: its increasing rate is connected to growing urbanization and changing lifestyle habits (International Diabetes Federation, 2017).

Regular exercise, together with a healthy diet, represents the most important preventive factor for people at risk of type 2 diabetes. Exercise improves insulin resistance and blood glucose control, increases balance and coordination, enhances brain plasticity, cardiorespiratory endurance, and well-being. Exercise has beneficial effects on the control of many factors related to diabetes (lipid profile, hypertension, and obesity; Tuomiletho et al., 2001; Lunghi et al., 2019a) and allows to reduce medication number and/or dosage (Balducci et al., 2012). The recommendations of the International Diabetes Federation (IDF) for managing type 2 diabetes encourage intensive therapeutic lifestyle changes such as exercise, the reduction of cholesterol, and the dietary intake of saturated fat (Aschner, 2017). More specifically, moderate aerobic physical activity such as walking for at least 150 min per week at intervals of no longer than 48 h was recommended. Resistance exercise such as moderate weightlifting or yoga can also be included. A more intensive physical activity program including at least 275 min per week may be needed to assist weight loss and avoid regaining it (International Diabetes Federation, 2017).

Although the literature is very large and the benefits of exercise are now well known (Lunghi and Sale, 2015; Tomas-Carus et al., 2016; Podolski et al., 2017; Lunghi et al., 2019b), inconsistent findings were sometimes reported (Zhao et al., 2018; Cooke et al., 2020; Dyer et al., 2020).

Exercise can influence cognitive functions by increasing brain activation and cerebral blood flow and perfusion (Rooks et al., 2010; Dupuy et al., 2015). Exercise increases (on average of one-half standard deviation) cognitive performance, independently of the cognitive task, the characteristics of participants, and the training method (Colcombe and Kramer, 2003). Executive function enhancement was reported after 6 months of aerobic training (Baker et al., 2010), while functional plasticity of response inhibition process improved after 12 months of resistance training (Liu-Ambrose et al., 2012). The engagement in simultaneous exercise and cognitive training (dual-task training) has been shown to improve cognition beyond the effects of the single underlying components (Cooke et al., 2020).

T2DM patients show an incidence double of cognitive impairment compared to non-diabetic adults (Lyu et al., 2020). In several cognitive domains as attention, processing speed, visuospatial abilities, memory, executive functions, and semantic fluency, poor performances in T2DM patients were often reported (van den Berg et al., 2009; Palta et al., 2014; Fava et al., 2017; Zhao et al., 2018; Sun et al., 2020). Neuropsychological cross-sectional studies (Manschot et al., 2007; Brundel et al., 2010) and longitudinal studies (van Elderen et al., 2010) found brain atrophy and white matter loss in patients with T2DM. More recently, systematic reviews and meta-analyses were also conducted, confirming these findings (cfr. Sadanand et al., 2016; Zhao et al., 2018; Cooke et al., 2020). Despite the increasing evidence, to date, the exact underlying mechanisms explaining cognitive dysfunction in T2DM remain unclear.

Exercise has been supposed to improve cognition by different mechanisms, directly or indirectly connected to glucose metabolism control, as increased synaptogenesis and neurogenesis, enhanced cerebral perfusion, reduced inflammation, increased availability of neurotrophins and neurotransmitters, and reduced cerebral atrophy (Tomas-Carus et al., 2016; Cooke et al., 2020). Thus, exercise may be useful to improve cognitive processes as executive functions and to reduce cognitive impairment (Secher et al., 2008; Baker et al., 2010; Kim et al., 2011; Zhao et al., 2020); however, in T2DM patients, impaired cerebral blood flow and oxygenation during exercise were reported (Kim et al., 2015; Vianna et al., 2015), producing relevant costs in addition to the well-known benefits.

A similar pattern was also observed in response to stimulation of metaboreflex (Delaney et al., 2010; Crisafulli, 2017) generated by metabolites accumulating in the muscle during contraction (Boushel, 2010). Muscle metaboreflex activated by metabolites accumulating in the muscle during contraction can enhance similarly the reduction of cerebral oxygenation (COX) and can impair cognitive functions and produce early fatigue (González-Alonso et al., 2004; Rasmussen et al., 2010). Therefore, in T2DM patients, the overlapping of a high-demand cognitive task to exercise could undermine the optimal neuronal environment. In a previous study conducted with patients suffering from metabolic syndrome (MS), we have observed that the connection between a concurrent mental task and metaboreflex can hesitate in a reduction of COX and in a deterioration of cognitive performance (Guicciardi et al., 2019; Doneddu et al., 2020).

Moving from these premises, we want to explore the contribution of affective states in their interplay with exercise, metaboreflex, and cognitive performance in a group of T2DM patients. Affective responses to exercise, as positive feelings or negative thoughts, were already investigated in T2DM patients, mainly to explain low adherence and retention rates to exercise (Guicciardi et al., 2014a) or to assess the feasibility and efficacy of specific exercise programs, as high-intensity interval training (Terada et al., 2013). However, more recent studies pointed out that affective states can be considered as regulators of exercise performance (Hartman et al., 2019).

Since the results obtained in the laboratory are often not easily generalizable to everyday life, we have also considered the assessment of the stage of exercise adoption, which has been proven to be a useful tool to target exercise interventions in T2DM patients (Kim et al., 2004; Kirk et al., 2010). Namely, we contrasted the two stages of preparation and action, which were considered critical to adopt an active lifestyle by individuals suffering from T2DM (Guicciardi et al., 2014b).

Thus, the present study intends: (a) to extend previous findings obtained with MS patients to a sample of T2DM people and (b) to investigate in an explorative way the contribution of affective variables (i.e., adoption, feelings, and thoughts toward exercise) as moderators of the relationship between cognitive performance and exercise in a group of T2DM patients.

MATERIALS AND METHODS

Participants

A group of 12 T2DM patients was enrolled [five women, mean ± standard deviation (SD) of age 49.5 ± 10.0 years] on the basis of the following criteria: clinical history of T2DM for

at least 1 year (range 1–6 years), stable metabolic condition (HbA1c level <9% at the time of the study), and absence of signs or symptoms of peripheral neuropathy. All patients were on medication with oral hypoglycemic agents; 11 with insulin (**Table 1**).

Instruments

The Exercise Thoughts Questionnaire (ETQ; Kendzierski and Johnson, 1993) measures by 25 items how frequently exercisers have exercise avoidant thoughts. Participants respond to a 5-point Likert scale with 5 anchored by "all the time" and 1 anchored by "not at all." Typical items include "I have not got time," "I'll do it tomorrow," and "I'm too busy." This instrument was already used to assess negative thoughts toward exercise in T2DM patients (Guicciardi et al., 2014a).

The Exercise-Induced Feeling Inventory (EFI; Gauvin & Rejeski, 1993) measures by 12 adjectives four feeling states: revitalization, tranquility, positive engagement, and physical exhaustion. The items are rated on a 5-point scale from 0 to 4, where 0 stands for "do not feel at all" and 4 stands for "feel very strongly." This instrument was already used to assess positive feelings toward exercise in people at risk for T2DM (Masters et al., 2011).

The stage of exercise adoption (SEA) was assessed by asking participants to choose which of five statements, each representing a stage of change, described their current exercise commitment (Marcus et al., 1992). The stages of change can be distinct on: precontemplation (not regularly physically active and no thought to become active in the next 6 months); contemplation (not regularly physically active but aiming to start in the next 6 months); preparation (doing some physical activity but not enough to meet the description of regular physical activity); action (regularly physically active but only begun in the last 6 months); and maintenance (regularly physically active for more than 6 months). This instrument was already used to assess exercise adoption in T2DM patients (Kirk et al., 2010; Guicciardi et al., 2014b).

The Bivalent Shape Task (BST; Esposito et al., 2013) is a simple and fast nonverbal measure of cognitive interference and suppression that requires the participant to determine whether a shape at the center of the screen is a square or a circle. Two response targets are provided below the stimulus, one shaped as a circle and one as a square. The target circle is always on the left, and the square is always on the right. The participant, equipped with a mouse, is asked to click the response target corresponding to the center of the screen stimulus shape, ignoring stimulus and target color. The stimulus shape is presented in red, blue, or an unfilled black outline; response targets can be presented in red or blue. Three trial types exist: neutral (black or white stimulus); congruent (the stimulus color matches the response target color); incongruent (the stimulus color mismatches the response target color). The task was performed using an open source programming language (cross-platform) created to implement psychological tests. The response times were recorded in ms. The BST was already used as a mental task in a group of adults suffering from MS (Guicciardi et al., 2019).

The near-infrared spectroscopy (NIRS; Nonin, SenSmart X-100, Plymouth, MN, USA) was used to assess COX, providing a measure of oxygenated hemoglobin (Hb) in the brain tissue. NIRS was already used to assess COX during mental tasks (e.g., calculation), BST interference tasks, or Stroop tests in the general population (Plichta et al., 2006; Ferreri et al., 2014) and in MS patients (Guicciardi et al., 2019; Doneddu et al., 2020). Researchers placed two NIRS sensors in the subject's right and left sides of the forehead above the eyebrow (between Fp1 and F3 regions, international EEG 10–20 system) and adjusted according to the stronger signal. COX variations are representative of cortical activation (Strangman et al., 2002). Researchers considered the relative changes of NIRS signals vs. the baseline values; indeed, the absolute concentration of Hb cannot be obtained, since the path length of NIRS light within the brain tissue was unknown.

TABLE 1 | Descriptive statistics of the sample.

Variables (range)	*Mean*	*SD*
Age	49.50	10
BMI	30.54	5.78
Blood pressure (max)	123.75	14.94
Blood pressure (min)	82.08	10.54
Plasma glucose	106.58	12.96
HbA1c	6.42	0.73
Duration of diabetes (years since diagnosis)	3.17	1.58

BMI, body mass index; HbA1c, glycated haemoglobin.

Procedure

All participants, after a medical examination, were assigned in a random order to five sessions. All sessions lasting 12 min were composed of four blocks (3 min per block) spaced by a recovery of 15 min (cfr. Guicciardi et al., 2019, and Doneddu et al., 2020, for more details):

a. BST session comprises a rest period of 6 min, 3 min of mental task and 3 min of further recovery.
b. Control exercise recovery (CER) session comprises a rest period of 3 min, 3 min of rhythmic (i.e., 30 compressions/min) dynamic handgrips in the nondominant hand using a dynamometer, a rest period of 3 min.
c. Post-exercise muscle ischemia (PEMI) session comprises 3 min of resting, followed by 3 min of exercise, as in the CER session, 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. Three minutes of recovery was further allowed after the cuff was deflated, for a total of 6 min of recovery. This maneuver has been demonstrated to be capable of eliciting the metaboreflex-induced hemodynamic stimulation and able to detect cardiovascular abnormalities (Crisafulli, 2017).
d. CER + BST session comprises a rest-exercise protocol (the same used for CER). The exercise phase was followed by a BST session and a recovery period each for 3 min.
e. PEMI + BST session comprises the rest-exercise protocol utilized for PEMI, followed by a block including both PEMI and BST. Finally, the session was concluded with 3 min of recovery.

This study was designed according to 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 subjects gave written informed consent in accordance with the Declaration of Helsinki.

Data Analysis

Only data relating to sessions where BST was included were analyzed (BST, CER + BST, PEMI + BST). A preliminary check of data was executed (Kolmogorov-Smirnov test) to determine whether variables were normally distributed. After controlling for age and body mass index (BMI), repeated measures analyses were carried out to assess: (a) response times (ms) on BST and (b) change in COX (% from rest). Further explorative analyses were conducted on affective response test scores using a repeated measures ANCOVA with the individual's stage of exercise adoption as an independent variable and the positive feeling state as a covariate.

Statistics were carried out utilizing SPSS ver. 24.0. A value of $p < 0.05$ (statistical significance) was set up in all cases.

RESULTS

Descriptive statistics are reported in **Table 1**.

After controlling for age [$F_{(2,20)} = 2.266$, $p = 0.130$, eta squared = 0.185] and BMI [$F_{(2,20)} = 0.547$, $p = 0.587$, eta squared = 0.052] through two ANCOVAs, repeated measures analyses showed that, overall, the three sessions with the BST (PEMI + BST, CER + BST, and BST) were not associated with differences on response times [$F_{(2,22)} = 1.715$, $p = 0.203$, eta squared = 0.135; **Table 2a**].

As for the BST performance, as expected, results showed a main effect of the type of trial variable, showing that participants performed significantly faster when the stimulus was presented in congruent trials, followed by neutral and incongruent ones [$F_{(2,22)} = 12.951$, $p = 0.000$, eta squared = 0.541] (**Table 2b**).

TABLE 2 | Response time mean and standard deviation.

		Mean	*SD*
a)	BST	853.19	133.77
	CER + BST	890.63	177.03
	PEMI + BST	861.17	178.86
b)	Congruent	843.18	155.76
	Neutral	872.67	148.43
	Incongruent	889.14	174.63
c)	BST Congruent	819.14	138.16
	CER + BST Congruent	867.43	181.16
	PEMI + BST Congruent	842.98	165.69
	BST Neutral	864.21	123.16
	CER + BST Neutral	887.03	176.91
	PEMI + BST Neutral	866.77	161.88
	BST Incongruent	876.57	150.48
	CER + BST Incongruent	917.42	181.34
	PEMI + BST Incongruent	873.77	213.27

BST, bivalent shape task; CER, control exercise recovery; PEMI, post-exercise muscle ischemia.

Moreover, only CER + BST [$F_{(2,22)} = 5.102$, $p = 0.015$, eta = 0.317] and BST [$F_{(1.318,22)} = 6.837$, $p = 0.140$, eta = 0.383] showed significant differences between congruent, neutral, and incongruent stimuli (**Figure 1**). Marginal mean comparisons with Sidak adjustment showed differences associated with congruent and incongruent stimuli for CER + BST ($p = 0.013$) and BST ($p = 0.011$) sessions and with neutral and congruent stimuli for BST ($p = 0.004$; **Table 2c**).

The COX expressed as the cerebral oxygenation percentage variation from rest level significantly increased during the third minute of all sessions. *Post hoc* analysis revealed that CER + BST ($M = 103.10$; $SD = 2.89$) and post-PEMI + BST ($M = 102.24$; $SD = 2.00$) showed more increases ($p > 0.05$) compared to BST session alone ($M = 100.36$; $SD = 1.10$).

To better understand these differences, the individual's stage in the exercise adoption (dichotomized in preparation/action) was added into the analysis, together with the positive feelings and the negative thoughts toward exercise. A correlational analysis (Spearman's rho coefficient) among all affective response scores showed a significant negative relationship between negative thoughts to exercise and stage in exercise adoption (**Table 3**).

After controlling with Mauchly's test that the assumption of sphericity had not been violated [$\chi^2_{(2)} = 0.911$, $p = 0.634$], an ANCOVA was performed using stage of exercise adoption as a group factor, response time at sessions as a repeated dependent variable, and positive feeling about exercise as a covariate. In relation to CER + BST session, a significant interaction effect did not emerge between the stage of exercise adoption and congruence, but the positive feelings were a significant covariate [$F_{(2,18)} = 3.714$, $p = 0.045$, eta = 0.292], suggesting that this affective variable represents a source of variability that might have an effect on the outcome.

DISCUSSION

The ability to exercise regularly is critical for functional independence and well-being of adults suffering from T2DM. Hence, identifying factors that influence exercise adoption and cognitive impairment among adults with diabetes has important clinical and public health implications.

Executive functions are necessary for behavior change and may have the potential to affect an individual's capability to successfully adopt and maintain exercise (Olson et al., 2017). Successful management of diabetes is determined by the implementation of strategies able to mitigate the impairment of executive functions (Zhao et al., 2020).

Exercise appears to be a useful tool for T2DM patients because it reduces cognitive impairment and diabetes complications. However, exercise adoption requires more time and deliberate effort than just diet modification or medications taking, and it is perceived as a difficult and significant modification of the way of life (Guicciardi et al., 2014a). Thus, is imperative to understand how to support these changes (Conversano, 2019) by identifying the psychological variables that facilitate exercise adoption and act as protective factors toward cognitive impairment.

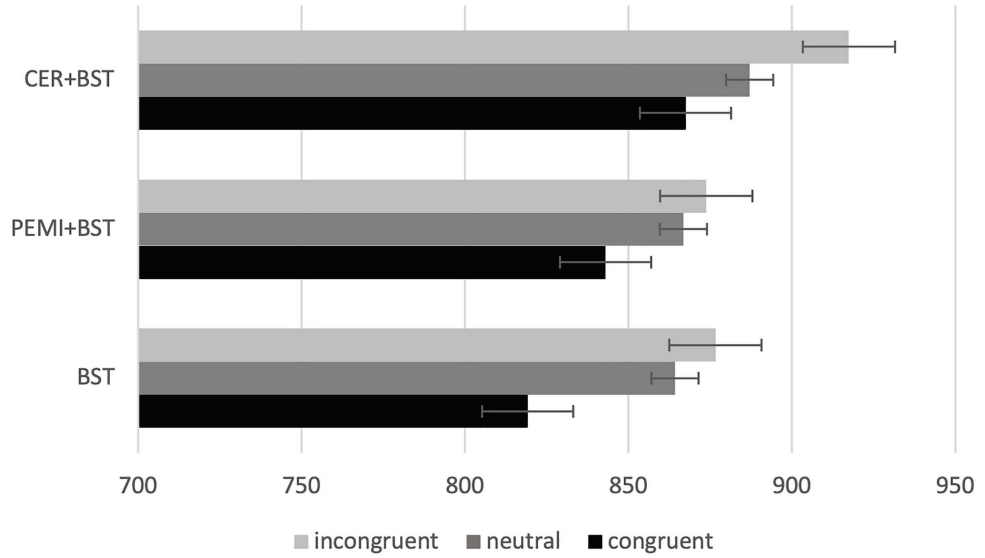

FIGURE 1 | Mean response time and standard error (bars) by sessions and trials. BST, bivalent shape task; CER, control exercise recovery; PEMI, post-exercise muscle ischemia.

TABLE 3 | Correlations among psychological variables.

	EFI	SEA	ETQ
EFI	1		
SEA	0.025	1	
ETQ	−0.444	−0.590*	1

EFI, Exercise-induced feeling scale; SEA, stage in exercise adoption; ETQ, exercise thoughts questionnaire.
*$p < 0.05$.

The main aims of the present study were: (a) to depict the cognitive performance in T2DM patients during exercise, with the association of a mental task (BST) to metaboreflex activated by means of the PEMI and (b) to extend the understanding of cognitive impairment during exercise in a group of T2DM people, introducing affective variables as feelings and thoughts toward exercise and the individual's stage in the exercise adoption.

With regard to cognitive performance, the mean response time did not differentiate the three sessions where a mental task was imposed. As expected, the T2DM patients, as well as the general population (Esposito et al., 2013), performed better with congruent trials compared to neutral and incongruent ones. However, when the interaction between type of sessions and type of BST trials was observed, T2DM patients performed worse in the CER + BST session, showing a linear increase of response times. These results are consistent with the neural inefficiency hypothesis (Zarahn et al., 2007), wherein higher brain activation is associated with worse task performance, suggesting that T2DM patients do not efficiently allocate cognitive resources to support high demanding mental tasks. Indeed, incongruent trials require participants to suppress the interferent immediate response to the stimulus color and consider only the relevant information (stimulus shape) to give the correct response. This interference does not appear in the PEMI + BST session and in the BST alone session, where the mean response time for incongruent stimuli was equal to neutral ones. Similar findings were also reported by Holtzer et al. (2018) using a dual-task walking with T2DM older adults.

The capacity to suppress the immediate response is crucial to manage T2DM because the acquisition of new behavior requires the inhibition of a habit (e.g., sitting after meals) and replacement with a healthier behavior (i.e., going for a walk; Settineri et al., 2019).

This impaired capacity is more amazing because CER + BST and PEMI + BST sessions showed a similar increase of COX compared to BST alone, confirming that both implicate a metabolic expenditure involving equivalent levels of sympathetic tone (Crisafulli, 2017).

Feelings about exercise seem to offer a supplemental explication of this phenomenon because only in the CER + BST session do positive feelings affect mean response times. Ratings of pleasure-displeasure were already used as indicators of the severity of the homeostatic perturbation during exhaustive exercise (Hartman et al., 2019). Studies conducted in the healthy population indicate that changes along the dimension of pleasure-displeasure can be considered the main channel by means of homeostatic perturbations entering consciousness and dictating corrective action, as slowing down or stopping exercise (Damasio and Carvalho, 2013). However, to date, to the best of our knowledge, this is the first time that affective responses and cognitive performances were jointly investigated during exercise in T2DM patients. The different contributions of positive feelings to cognitive performance claim for a deeper analysis of affective process and open new perspectives on exercise

prescription and self-care in T2DM patients (see Martino et al., 2020, for a similar suggestion).

Although structured exercise interventions have been shown to be effective in increasing physical activity levels and improving cardiovascular fitness and glycemic control during the intervention period, there is little evidence that these strategies have effects in the long run, if people are not supported in changing their habits. However, to support some form of lasting change, it is necessary to know what mechanism can counteract the emotional stress experienced by T2DM patients during exercise (Armstrong and Sigal, 2015; Guicciardi et al., 2015) and in the course of daily life (Tomas-Carus et al., 2016; Martino et al., 2019). Positive feelings appear to play a protective role against the distress caused by exercise in T2DM patients who are performing, in an experimentally controlled condition, an attentional interference task, but further studies are needed to assess their contribution in everyday life.

Data related to the effects of experimental sessions on response times were examined and used to infer information about the brain mechanisms associated with mental task while conducting an exercise. The different mean response times for the congruent and incongruent stimuli in two equivalent conditions of metabolic expenditure (CER + BST and PEMI + BST) should be emphasized: while in the PEMI + BST, there is not a significant difference between congruent and incongruent trials' response times, in the CER + BST, the incongruent trials are answered slower than the congruent ones. It seems that participants have experienced the difficulty of the coupling of exercise and cognitive demand more in a condition than in the other. While CER + BST is an explicit condition of physical exercise, the PEMI + BST emulates the metabolic expenditure produced by exercise by means of the enhancement of the sympathetic tone and sympathetic nervous system (SNS) activity (Boushel, 2010). A possible explanation of our findings is that the disadvantage of the most demanding trial condition (the incongruent one) becomes more evident when an exercise is explicitly required. Moreover, it is noteworthy that the contribution of positive feelings, as already noted, appears only in the CER + BST session as if the affective response to exercise manifests itself only when the brain predicts that some perturbation will change the general homeostasis. This tentative hypothesis is further supported by findings that the ratings of perceived exertion are mostly unrelated to indices of metabolic strain (e.g., heart rate, blood lactate, and respiratory frequency) at low intensities (Hartman et al., 2019). The results of our exploratory study are promising, but the small size of our sample does not authorize more speculations. More studies, as randomized controlled trials and large-scale studies, also looking for gender differences and age-related effects, should be developed to investigate the mechanisms that regulate the relationships between affective response to exercise, consciousness, COX, and cognitive performances in T2DM patients.

Limitations of the Study

The study suffers some limitations. This was a cross-sectional study with a small sample size and without a randomized control group. However, this study extends a previous one conducted with an MS group and a matched control group, in which the same experimental setting was used. The indirect comparison between our consecutive studies dampens but does not eliminate this flaw. The BST was already used with MS patients, but further studies are necessary to validate this task with T2DM patients. NIRS, compared to others neuroimaging techniques, suffers from low spatial resolution, but its sensitivity to measure subtle changes in COX in the normal population and MS patients during cognitive tasks and exercise already has been proven.

In conclusion, patients with T2DM achieve worse cognitive performance when incongruent stimuli were presented during exercise, but not when the same stimuli were presented in a condition of equivalent metabolic expenditure. Moreover, positive feelings about exercise seem to modulate cognitive performance in T2DM patients in response to high requiring stimuli, only when an attentional task was associated with a deliberate practice.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the University of Cagliari. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

The original study design was made by AC and MG and was discussed with the other authors. AD and DF performed the experiments and collected and analyzed, respectively, functional and psychological data. RF conducted the formal analysis. MG and AC wrote, reviewed, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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MINI REVIEW
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Psychological Aspects of Students With Learning Disabilities in E-Environments: A Mini Review and Future Research Directions

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What are the main learning difficulties or advantages encountered by students with learning disabilities (LDs) within e-environments? As a result of the Covid-19 emergency, e-learning is being increasingly used to support students' learning processes. A number of countries closed their schools altogether, so face-to-face lessons were and have been replaced by distance lessons. A search of current literature via Scopus, Eric and Google Scholar electronic databases was conducted according to Prisma Guidelines. Other sources of literature were also considered, starting from the references in the full text of the articles consulted. We used the following search keywords: "LDs" combined with the "AND/OR" Boolean operator and "e-learning platforms," "well-being," "psychological factors," "emotional distress," and "self-regulation." One body of literature highlights the lack of inclusive accessibility standards and a lack of attention to specific tools for addressing LDs, which causes students to develop high levels of stress/anxiety and emotional distress, in addition to low levels of well-being, self-esteem and self-efficacy. Another area of literature looks at how students can develop high levels of self-regulation and emotional awareness, as well as high levels of inclusion. Results are discussed in terms of the promotion of e-learning that focuses on the psychological well-being of students and teachers use of technological tools.

Keywords: e-learning, psychological well-being, emotional distress, self-regulation, learning disabilities

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INTRODUCTION

The forced interruption of face-to-face teaching due to the worldwide outbreak of Covid-19, has significantly reactivated the debate on the concrete effectiveness and functionality of e-learning courses. Specifically, our goal was to better understand the psychological effects and efficacy of the current massive use of the e-environments on students with learning disabilities (LDs) (Viner et al., 2020). Literature shows a variety of ways to define e-learning. For example, Cidral et al. (2018) define e-learning as a web-based learning system for the dissemination of information, communication, and knowledge for education and training. Until 2002, Eletti had affirmed that e-learning is a new type of training, a new teaching system that allows you to follow and above all personalize learning. The services and tools used allow for continuous contact with the "student". In addition, a platform and an interface built *ad hoc*, adapting the contents, allows to model the

teaching on the user's needs (Eletti, 2002). Thus, in light of the massive use of e-environments, there is a definite need to question how effective these tools are for students with LDs. According to international diagnostic criteria, LDs are an overarching group of neurodevelopmental disorders comprising different learning disorders that affect primary and/or secondary academic abilities and a child's overall capabilities (American Psychiatric Association, 2013; Schulte-Korne, 2014). Children with specific LDs are a rather heterogeneous group, both with regard to specific academic abilities such as listening, thinking, reading, speaking, writing, calculating, and spelling (Sorrenti et al., 2019), as well as to their neuropsychological and functional profiles. For example, they may have impairments affecting different cognitive and neuropsychological abilities (working memory), long-term memory (implicit and explicit memory), attention (selective and sustained), and linguistic, praxis, visuospatial, problem solving, and/or executive abilities (Petretto and Masala, 2017; Visser et al., 2020), etc. Moreover, there is general agreement on the association between LDs and other neurodevelopmental disorders (ADHD and specific language disorders); LDs typically occur in individuals of normal intelligence (Sorrenti et al., 2019). A body of studies indicates a relationship between children's LD and poor social relations in school (Walker and Nabuzoka, 2007), this aspect is confirmed also in the University context (Filippello et al., 2019). Literature shows a relationship between LDs and internalizing (depressive and anxiety disorders) and externalizing disorders (conduct disorders) (Frith, 2013; Bonifacci et al., 2016; Panicker and Chelliah, 2016; Visser et al., 2020). If LDs are not adequately treated, they can evolve over time, potentially resulting in forms of psycho-social maladjustment (Sorrenti et al., 2019). Regarding the use of e-learning, only a small number of studies have addressed these psychological factors and consequences, and there are few studies which have directly examined the quality of life of students with LDs, or the quality of interpersonal relationships (parents, teachers, and peers). In this mini-review and according to previous research in the field, we analyze these aspects and focus our attention to the following questions:

(1) What are the effects of the use of e-learning on psychological well-being?
(2) What are the effects of accessibility standards in promoting inclusion and in reducing stress, anxiety and emotional distress among students with LDs?

METHODOLOGY

A search of current literature using Scopus, Eric and Google Scholar electronic databases was conducted according to Prisma Guidelines (Moher et al., 2015). Other sources of literature were also considered, starting from the references in the full texts of the articles examined. We used the following search keywords: "LDs" combined with the "AND/OR" Boolean operator and "e-learning platforms," "well-being," "psychological factors," "emotional distress," and "self-regulation". Applying a systematic procedure, literature was then selected and results were charted and analyzed. The following inclusion criteria were established: papers on the use of e-learning with LD; on the relationship between e-learning platforms and related psychological aspects (self-esteem, emotional distress, and self-regulation); written in English and published from 2015 to 2020. The following exclusion criteria were applied: systematic reviews; papers on the use of e-learning without LD. On the basis of the research questions and the literature considered, we chose a minireview. For this reason the data will be presented as a narrative review.

RESULTS AND DISCUSSION

In the first part of the search, two independent assessors found 53 articles. Applying our inclusion and exclusion criteria, after reading the abstract, 27 articles were considered. After reading the full texts, 4 further articles were excluded, thus a final group of 23 articles were considered (**Table 1**). As expected, in literature, regarding the definition of "e-learning", we found different systems and tools (platforms, devices, web materials/sites, Learning Content Management Systems, ICT, etc.). According to Bjekic et al. (2014) we categorized the different definitions in two groups. The first group refers to the use of Assistive Technology (AT) (hardware or software, used to increase, improve or maintain capabilities of persons with LDs aimed to support and/or increase learning). The second group of e-learning refers to a system of procedures, processes and instructional materials that supports learning. Moreover, we considered a difference between e-platforms and ICT tools (Salehi et al., 2015; **Table 2**).

The papers showed a certain amount of heterogeneity in their definition of LDs. Some authors proposed a specific definition (Chen et al., 2015; Richardson, 2015; Shonfeld and Ronen, 2015; Straub and Vasquez, 2015; Benmarrakchi et al., 2017; Sharabi et al., 2016; Adam and Tatnall, 2017; Vasalou et al., 2017; Lambert and Dryer, 2018; Lipka et al., 2019; Ziadat, 2019), while others proposed a general reference to Special Educational Needs or used the World Health Organization definition of Disability (World Health Organization, 2001; Berizzi et al., 2017; Naumova et al., 2017; García-González et al., 2020). Some papers reported the definition of LD based on international diagnostic criteria, others described specific national law/s or references (Sharabi et al., 2016). Moreover, with regard to sample recruitment, some authors chose samples consisting of different groups of students with other kinds of disabilities and then specified the number of students with LDs (Richardson, 2015, 2016; Shonfeld and Ronen, 2015; Terras et al., 2015; Benmarrakchi et al., 2017; Sharabi et al., 2016; Alamri and Tyler-Wood, 2017; Berizzi et al., 2017; Kent et al., 2018; Lipka et al., 2019; Ouherrou et al., 2019; García-González et al., 2020); while in other papers, the sample is made up only of students with LDs (Chen et al., 2015; Straub and Vasquez, 2015; Vasalou et al., 2017; Lambert and Dryer, 2018). Regarding the level of schooling, about 1/2 of the studies focused on University environments (Richardson, 2015, 2016; Terras et al., 2015; Alamri and Tyler-Wood, 2017; Naumova et al., 2017; Kent et al., 2018; García-González et al., 2020) and the

TABLE 1 | Characteristics of papers which met the inclusion criteria.

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
1. Adam and Tatnall, 2017	This study investigates whether, and if so how, ICT could be used to support school communities involving students with learning difficulties, and whether it could help these students with their learning in two special School settings	Australia	T/P	No	-Case studies -Interviews with the School Principal, Teachers and Parents	ICT in teaching -ICT was used predominantly to reinforce language and numeracy skills -Classrooms are equipped with an electronic whiteboard and each student has access to a notebook computer and iPad. ICT offered opportunities for students to use technology that would improve their literacy output, access and exposure to technology as well as increasing engagement and provides evidence that scaffolding with a direct teaching approach enhances the learning outcomes of LD students.	-180 students in the first school -About 400 students in the second school (n.s.)	S	n.s.	n.s.	-Attainment in skills and academic knowledge -use of ICT enhances LD students' independence and equips them with adequate skills which should allow them to continue with further study through various pathways and to move into a normal work environment
2. Alamri and Tyler-Wood, 2017	This study investigates which factors associated with learners with disabilities impact student outcomes in an online learning -Environment Successes and struggles in an online setting -Nature of interaction between students with disabilities and instructors	USA-midwest	S	No	Electronic survey of 20 questions	For online courses, the interaction can take place through the use of both synchronous tools (videoconferencing, audio stream, online chat sessions) and asynchronous tools (e-mail, discussion boards).	40 (4LD, 10 ADHD)	U	LD and ADHD	18–58	-Social presence, -interpersonal relationships -Achievement -Satisfaction -different types of interactions in online learning: learner–interface interaction, learner–content interaction, and learner–learner interaction.

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
3. Baharuddin and Dalle, 2019	The study uses a four-phase iterative process to develop and analyze a prototype eLearning system: understanding the problem, designing the system, developing the system, and gathering user feedback	Indonesia	T/S	No	Interviewed observation during the use of ICT	Computer connected to the Internet, virtual classrooms	17 teachers (n.s.)	S	n.s.	n.s.	Communication Attendance Reasonable accommodations Knowledge and competencies of teachers
4. Benmarrakchi et al., 2017	This study investigates the potential benefits offered by the use of Information and Communication Technology (ICT) to support dyslexic students by considering their preferred learning styles. Based on the results of the analysis of learning styles differences, the authors introduced an adaptive mobile learning to support and promote learning for dyslexic students.	Morocco	S	No	Questionnaires	ICT (digital technologies Multimedia applications) adaptive mobile learning	28 (8)	PS	dyslexia	8–10	Learning styles (description of the attitudes and behaviors, which determine an individual's preferred way of learning VAK learning style model is based on three main sensory receivers: visual (V), auditory (A), and kinesthetic (K). - 'cycle of learning', four-stage cycle of learning: abstract conceptualization (AC), concrete experience (CE), active experimentation (AE), and reflective observation (RO).

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
5. Berizzi et al., 2017	This study investigates the effect of an attributive-metacognitive training on attributional style of students with Special Educational Needs (SEN), proposed by a elearning platform	Italy	S	Yes	Questionnaires	ICT (e-mail, Skype network conversations, videoconferencing, e-learning platforms, such as Moodle, Edmodo, and others)	30 students with special educational needs (30)	SS	24 dyslexia 6 ADHD	11–15	Metacognition Self esteem Self efficacy Locus of control
6. Chen et al., 2015	This study aims to explore the learning experience of learners with dyslexia when reading passages using different online reading affordances to derive some guidelines for dyslexia-friendly online text.	Malaysia	S	Yes Web site accessibility guidelines and role of engagement	Qualitative multiple-case study	Web sites The use of online learning is appropriate for learners with dyslexia as this delivery mode allows self-paced learning and affords multimodal technologies that have the potential to settle dominant deficit models of dyslexia	12 (12)	SS	Dyslexia	14–18	Online reading affordances Perceived learning behavioral engagement (BE), cognitive engagement (CE) as well as affective engagement (AE) web accessibility guidelines for users with dyslexia
7. García-González et al., 2020	This study investigates how students perceived access to higher education -Role of barriers	Spanish	S	Yes	Focus group and interviews Discourse analysis	Personal Learning Environments PLE WEB	16 (3)	U	Dyslexia	20–29	Web or computer barriers, Learning barriers, burocratic barriers, architectural barriers, social barriers

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
8. Kent et al., 2018	This study investigates both the attitudes of students with disability towards disclosure of their disabilities and their experiences ofstudying online and accessibility of online learning materials	Australia	S	Yes Accessibility on web materials Need for a more interest toward Universal Design	Online survey	E-learning in open university	2000 students with disability (16,3% with LD)	U		Mean age 36	Accomodations and disclosure of disabilities and the difficulties for students to disclosure their disabilities, even if this makes difficult to personalized accomodations.
9. Lambert and Dryer, 2018	This study investigates the effects of learning challenges on online learning environments on the quality of life of students with learning disabilities	Australia	S	Yes	Semi-structured interview	Online learning environments	8 (8)	U	Dyslexia	21–43	Stress, quality of life, anxiety, self esteem
10. Lipka et al., 2019	This study investigated how students and instructors perceived the instruction in adapted courses in post secondary school students	Israel	S/T	No	Semi-structuredinterviews	Adapted courses	1000 (5)	U	LD and ADHD	20	Perception of teaching Locus of control emotional support
11. Naumova et al., 2017	This study investigates an integrated educational methods of training matching the features of disabled students. The technology includes both traditional and innovative methods of training	Russia	S	Yes	n.s.	Adapted courses with online web content. Information technologies Web content has to be available for a wide range of users with health limitations.	6 (n.s.)	U	n.s.	n.s.	Educational Motivation Interpersonal Relationship
12. Nieto-Márquez et al., 2020	This study investigates effects of digital teaching on metacognitive skills	Spain	S	No	Questionnaire	Digital teaching platform called Smile and Learn,	130 (n.s.)	PS	n.s.	8	Metacognitive skills

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
13. Ouherrou et al., 2019	This study explored the benefits of ICT use to identify the ways in which emotions are involved during the learning process in Virtual Learning Environments (VLE)	Morocco	S	Yes		ICT Virtual learning environment Artificial intelligence Educational games	42 (14)	PS	LD	7–11	Affective state Emotions Facial expression recognition
14. Rice and Carter, 2016	This study investigates how practicing teachers provided self-regulation strategies to students with disabilities in a fully online learning environment. In this context, the teachers intended to offer self-regulation strategies to students, but they were largely unable to do so.	Kansas	T	Yes		E-learning environment	Teachers (n.s.)	S	n.s.	n.s.	Emotional demands Selfregulation In students with disability
15. Richardson, 2015	This investigation studied attainment in students with dyslexia or other specific learning difficulties who were taking modules by distance learning with the Open University in 2012. Students with dyslexia or other specific learning difficulties who had no additional disabilities were just as likely as nondisabled students to complete their modules, but they were less likely to pass the modules that they had completed and less likely to obtain good grades on the modules that they had passed.	UK	S	Yes		Distance learning in open university computer-based support, particularly CD-ROMs, dedicated websites and computer-mediated conferencing	4961 (n.s.)	U	Dyslexia	21–60	attainment

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
16. Richardson, 2016	This study examined the experiences of students taking the same courses in the humanities by distance learning when tutorial support was provided conventionally (using limited face-to-face sessions with some contact by telephone and email) or online (using a combination of computer-mediated conferencing and email).	UK	S	yes		In distance learning, the curriculum was traditionally provided through correspondence materials. Nevertheless, most distance-learning institutions use various kinds of personal support in trying to narrow what Moore (1980) called the "transactional distance" with their students, most commonly through regular albeit limited tutorials. In recent years, there has been an increasing use of information technology in distance education, with a move from paper-based to electronic materials accompanied by a move from face-to-face to online tutorial support	292 (24)	U	Dyslexia	n.s.	The results showed that, given a choice between face-to-face and online tutorial support, students with and without disabilities were equally likely to choose online support rather than face-to-face support
17. Sharabi et al., 2016	This study investigates personal resources, loneliness, and academic self-efficacy among college students with and without LD in smartphone and internet use	Israel	S	No	Questionnaire	Smart phones Internet	178 (59)	Transition to college	n.s.	24 mean age	Coping, Self-efficacy Predictors of loneliness Hope, optimism Sense of coherence

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
18. Shonfeld and Ronen, 2015	This study investigates how adapting the online course by using information and communication technology following formative assessment will improve students' self-learning ability as well as broaden their science knowledge, their lab performance and teaching skills. The study was focused on preparing K-2 pre-service teachers	n.s.	S	No	Questionnaires and interviews	Online learning as a teaching tool, the challenge of adapting a course for three groups of students: students with learning disabilities, excellent students, and average students	121 (25)	U	n.s.	n.s.	The online course was based on the Highlearn platform which enabled ICT learning synchronously through InterWise. The course included peer teaching: students conducted group discussion and peer feedback; individual monitored learning. All students were instructed by the lecturer in developing
19. Smith et al., 2016	This study investigated parent perceptions and experiences regarding fully online learning for their children with disabilities	Kansas	P	Yes	Interviews	Online learning in online schools	18 (Parents of children) (7)	S	Learning disabilities	n.s.	Parental role on online learning Communication
20. Straub and Vasquez, 2015	This study investigates online writing instruction for students with learning disabilities (LDs) using synchronous online collaborative writing software to investigate effects of self-regulated strategy development for strategy instruction in persuasive writing.	USA Florida	S	No	n.s.	Writing Instruction Online	4 (4)	S	n.s.	adolescent	Self-regulated strategies development

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
21. Terras et al., 2015	This study investigated how online learning may afford students with disabilities enhanced opportunities for academic success. In this study, the authors interviewed 11 graduate students to determine their experiences with disability accommodations in online courses and their perceptions of the relationship between those accommodations and their academic success.	North Dakota	S	Yes	n.s.	Accommodation in online courses Since students with disabilities may have difficulty concentrating, staying on task, and adhering to a schedule, online settings (particularly those that are asynchronous) allow students to access courses anywhere, anytime, and any place and provide "the personalized time they need to think, process, and respond".	11 (4 LD 2 ADHD)	U	Learning disabilities ADHD	22–55	Disability accommodations in online courses students responsibility instructor responsibility University responsibility
22. Vasalou et al., 2017	This study investigates the case of a digital game called Words Matter. The game was designed for children with dyslexia and was informed by principles from casual games and evidence-based practice from special education. Focusing on the game play of two groups of children, we employ a systematic thematic analytic approach on videos of children's verbal and non-verbal interaction triangulated with their game logs, concentrating on the nature of student-student as well as student-tutor social interactions.	UK	S	No	Case studies	Drill and practice digital games-based learning Games-based pedagogies for students with special education needs	8 (8)	S	Dyslexia	11–12	Motivation Engagement on learning Social engagement Self-esteem Personal identity Peer tutoring

(Continued)

TABLE 1 | Continued

Author(s), Year	Topic of paper	Country/ Countries	Point of view	Accessibility	Methodology	Definition e-learning platforms, instruments and/or devices used	Total no. of subjects (Total no. of subjects with LD)	Type of school/ university	Kind of LD	Age range	Assessed Variables
23. Ziadat, 2019	This study investigates the impact of e-Learning on the development of academic and social interaction skills among students with learning disabilities in Jordan from the perspective of their teachers	Jordan	T	No	n.s.	Multimedia and information technologies; as well as the use of the internet as a new technique of teaching, The internet has become one of the most important ways to make available resources and to share and acquire information. No common definition of the term e-learning.	100 teachers (n.s.)	S	n.s.	n.s.	Role of e-learning on the development of academic skills among students with learning disabilities Social interaction Social behaviour

Point of view: *Students (S), Parents (P), Teachers (T);* ***Type of school/university:*** *Primary School (PS), Secondary School (SS), High School (HS), University (U);* ***not specified:*** *n.s.; Special educational Needs/Special Education Needs: SEN.*

Accessibility: *Yes or No (considered/not considered in the article).*

other 1/2 examined primary and secondary schools (Chen et al., 2015; Straub and Vasquez, 2015; Benmarrakchi et al., 2017; Rice and Carter, 2016; Smith et al., 2016; Adam and Tatnall, 2017; Berizzi et al., 2017; Vasalou et al., 2017; Baharuddin and Dalle, 2019; Lipka et al., 2019; Ouherrou et al., 2019; Ziadat, 2019; Nieto-Márquez et al., 2020). One paper focused on the transition from school to university (Sharabi et al., 2016). As expected, we also found a considerable heterogeneity in school settings, ranging from mainstream school/classrooms to special needs schools/classrooms, according to specific national and theoretical approaches and policies regarding the field of inclusion (see **Table 2**). Given that the countries in our sample ranged across Europe, United States, as well as Arab and Slavic countries, there was some diversity in the idea of inclusive policies for students with LDs. This is due to national differences regarding the issues of policies for students with LDs and, in general, for students with SEN. In some countries, there is an inclusion-based approach where students with LDs are placed in mainstream schools; in other countries there are special schools and special classrooms for them. In some countries, transition to complete inclusion is still ongoing (Lindsay, 2016; Norwich, 2016; Petretto et al., 2019; Pilia, 2019). While one of the papers described a specific experience in two special needs classes (Adam and Tatnall, 2017), other research papers concentrated on the use of specific e-learning approaches to designated groups of children with LDs or to all the children in the classroom in mainstream schools (Straub and Vasquez, 2015; Vasalou et al., 2017).

The approaches employed range from the use of specific devices and/or platforms, to the use of specific "reasonable accommodations" (such as font quality and sizes in the learning materials on the web or the use of specific support technologies) (Chen et al., 2015; Benmarrakchi et al., 2017; Rice and Carter, 2016; Alamri and Tyler-Wood, 2017; Berizzi et al., 2017; Ouherrou et al., 2019; García-González et al., 2020); or the use of software/games aimed to increase specific abilities in students with LDs (Straub and Vasquez, 2015; Vasalou et al., 2017). For university settings, some articles describe the experiences of so-called "Open universities" that have been based on distance learning methods since they started. With the development of ICTs, in the past few decades these universities have started to use e-learning platforms to contact students and to promote learning and social connections (Richardson, 2015, 2016; Kent et al., 2018). Their ongoing experiences focus mainly on the attainment of students with LDs as well as on the need to increase access to information and learning. Other studies focus on the need for dedicated online courses to specific categories of students, aiming at reducing barriers and distances and providing specific accommodations (Terras et al., 2015).

The age range in these university samples is very wide. From a positive perspective it can represent a sign of the wider opportunity for older people to access university courses. However, according to some studies, it could be also the sign of a lower and slower attainment of students with LDs in University (Richardson, 2015, 2016; Shonfeld and Ronen, 2015). The topics of attainment and achievement are interesting because even though some papers have discussed the risk of low achievement for students with LDs, other studies

have demonstrated the positive effect of accommodations and have showed examples of unexpected achievement by LD students (Shonfeld and Ronen, 2015). Another aspect is the fear of disclosure of their diagnosis by some students with LDs and the effects on their tendency to hide diagnoses rather than to communicate it, even when they should do so in order to define specific "reasonable accommodations" (Richardson, 2015, 2016; Terras et al., 2015). Although there may be increased student awareness of the need to disclose their diagnosis and the functional profiles that help to define a personalized approach that facilitates their access to learning and materials, some authors have highlighted the importance of further discussing the role of communication between teachers/instructors and students with LDs in the development of more comfortable learning environments and in the pursuit of shared learning and achievement aims (Terras et al., 2015).

Focus on Psychological Well-Being

Few studies have directly examined the psychological aspects of students with LDs in e-environments. Some papers have focused on psychological consequences of the intensified use of Information and Communications Technologies (ICTs); other papers instead focused especially on adults, addressing some psychological effects of e-learning procedures adapted to students with LDs. In their study, Ouherrou et al. (2019) highlighted the fact that the integration of ICTs in special needs education may have a positive impact on the emotional states of children with LDs, because they may experience fewer negative emotions than findings of current literature would suggest with regard to the presence of higher levels of negative emotions in the classroom. Vasalou et al. (2017) argued that a socially constructed view of digital games-based learning provides new opportunities for the support of children with dyslexia. Children spontaneously engage in "game talk" regarding game performance, content, actions and they strategically use their individual game experiences to express their personality and interact with their peers. Also, such experiences can help improve the intra-individual function by enhancing a child's self-esteem. The findings of Sharabi et al. (2016) supported earlier studies that assessed children and adolescents with LDs (Sharabi and Margalit, 2014), showing that college students with LDs possess lower levels of personal resources (sense of coherence, hope and academic self-efficacy) and suffer higher levels of social distress and loneliness than their peers. The loneliness factor was predicted by measuring online avoidance coping, their amount of smartphone use and by examining their personal resources, the use of ICTs may provide additional environmental conditions to enable youngsters to meet their emotional needs. At the same time, these opportunities may also be misused as avoidance coping and thus may contribute to increased loneliness and lower academic self-efficacy. Coherently with previous studies, Lambert and Dryer (2018) highlighted that

TABLE 2 | Papers which met the inclusion criteria in the school setting analyzed according to Bjekic et al. (2014).

School	E-learning (N Studies)		Limitations	Strenghts
	ICT	E-platforms		
Primary/Secondary School	4(3*)	8**(6*)	– Lack of interest: • technology in the development of student curriculum design framework for digital materials personalized paths parent's training in supporting children's e-learning experience	– Promotion of: • skills and academic knowledge educational outcome students'independence and self-regulation pathway for the transition from school to further study learning styles communication among children, teachers and parents metacognitive experience emotional well-being tutor/teacher scaffolding parents support
High school	1*	1*	– Lack of: • design interface appropriate online instruction strategies	– Promotion of: • tutor/teacher scaffolding social support stress and anxiety reduction
University		12 (3*)	– Lack of: • longitudinal studies self-regulation and emotional well-being	– Promotion of: • scaffolding (instructor-learner interaction) social support metacognitive interventions academic retention

**Presence of Assistive Technology.*
***Three studies with E-platforms and ICT.*

in high education the e-environment had a negative influence on the quality of life of students with increased stress and anxiety, the perception of feelings of inadequacy, a decrease in time available for other activities and personal relationships. The same authors also highlighted that for many students, the academic and emotional support provided by family and friends was a key factor in study success. Studies on the perception of the impact of e-learning on the development of academic skills and social interaction from the perspective of students and/or teachers showed that the quality of teacher-student relationships contribute to producing improvements in learning achievement (Alamri and Tyler-Wood, 2017; Lipka et al., 2019; Ziadat, 2019). Only a small number of studies have considered the role of parents. Smith et al. (2016) investigated parents' perceptions and experiences regarding exclusive online learning for their children with disabilities. The results showed that this experience altered parents' previous roles and that many parents were not equipped to take a teaching role due to lack of training, time, and other constraints. A parent-as-teacher role can negatively affect parent–child dynamics, leading to frustration for parent and child but full online learning requires increased parent–teacher communication. This increased level of interaction and the positive outcomes associated with the shared information enhanced a collaborative parent–teacher relationship. The use of ICT and e-learning can improve the learning of students with LDs only where a supportive context is present. The support provided by family, teachers and peers can create a protective factor which improves the well-being of students with LDs.

Focus on the Accessibility Standards and Emotional Distress

Many of the difficulties in designing e-learning courses are due to accessibility issues that can affect successful engagement (Draffan, 2012; Seale, 2013). The heterogeneity of the LD population entails great challenges to all parties involved in creating, managing and using e-learning content, tools and platforms with accessibility features (Guenaga et al., 2004; Baharuddin and Dalle, 2019). Some papers described the risks of a design approach based on a general and average idea of students without LDs (Kent et al., 2018). For Beacham and Alty (2006) the e-learning materials commonly employed were developed with the needs and capabilities of non-dyslexic learners in mind; clearly, resources do not generally take into consideration the individual learning approaches that these students manifest (Alsobhi and Abeysinghe, 2013; Chen et al., 2015; Luongo, 2018). Chen et al. (2015) also underline this point, observing that empirically derived guidelines for designing accessible online learning environments for learners with dyslexia are still scarce. The problem of accessibility is fundamental in e-learning design, as it is strictly linked to certain psychological factors that will affect students, like willingness to focus on learning, management of emotions and behavior, learning motivation, interest and self-regulation (Chen et al., 2015; Berizzi et al., 2017; Luongo, 2018). Existing literature provides clear evidence that text-based synchronous activities commonly used in education, like chat programs and videoconference, can create psychological and learning difficulties. However, only a small number of papers take into account the problems of students with LDs in collaborative environments (Luongo, 2018). Some papers focus on the positive aspects of the use of e-learning platforms in increasing accessibility to information and learning materials (Richardson, 2016), above all because participation in remote activities, like on-line forum discussions, improves the autonomy and self-regulation of students (Berizzi et al., 2017). These aspects are reinforced by continuous support of tutors and peers, and reflection on what has been done, the goals to be achieved, and ultimately the strategies to be adopted. Other articles described the possible role of a "universal design for learning approach" in the design of websites, web materials and e-learning platforms (Chen et al., 2015; Shonfeld and Ronen, 2015; Alamri and Tyler-Wood, 2017; Kent et al., 2018; Nieto-Márquez et al., 2020) in order to create environments that can be useful also for students with LDs.

CONCLUSION

This mini-review has attempted to analyze both the quality of life of students with LDs and their interpersonal relationships and the features of e-learning that can have positive and negative effects on them. The considerable heterogeneity of the articles we selected led us to the following reflections: we are aware that the heterogeneity could represent a limit but also an expected consequence of the chosen way of to explore a complex topic. Bearing in mind this issue, in a following article we will discuss the picture of the state of art that we derived from this minireview. In the near future, we will explore specific and more focused aspects, also with an attention on intervention aims. Two issues are emerged.

The first is how important online-support is to consolidate teacher-learner relationships, as it can affect a student's well-being and learning achievement. We know that e-learning is a psychological process supported by e-technology, and learning is a social activity. Understanding that it is socially constructed should ensure that e-learning is organized to promote participation, allowing all students to take part in all activities, thus enhancing cooperative-learning.

The second consideration regards the fundamental role of accessibility and "reasonable accommodations", which should lead to a reduction of emotional distress and promote positive psychological factors through full engagement with e-learning. In order to be effective, e-learning must go beyond simply digitizing books and ought to be designed carefully and appropriately for learners (Penna and Stara, 2007, 2010). What about the current and ongoing experience of the massive use of e-learning due to the COVID-19 outbreak? We agree with Al Lily et al. (2020),

who coined the term "Crisis Distance learning," that the current ongoing experience is different from previous ones, and that caution is needed before making any kind of generalizations from previous experiences. Nevertheless, some general considerations can be drawn for future research. It is necessary to encourage and maintain cooperative approaches in all spheres, including in the use of e-learning in school and universities, with particular attention on the quality of the relationships between all the people involved (students-teachers-parents-peers) and with an even more specific focus on the psychological needs of students with LDs. The improvement of e-learning systems designed with attention to the care and quality of relationships can promote well-being among all parties involved in the learning process.

AUTHOR CONTRIBUTIONS

All authors equally contributed to the design of the study. All authors have read and agreed to the published version of the manuscript.

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Psychological Factors as Determinants of Chronic Conditions: Clinical and Psychodynamic Advances

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The involvement of psychological factors in the etiology of chronic diseases is rousing the interest of the scientific community (Conversano, 2019; Martino et al., 2019b; Merlo, 2019; Lenzo et al., 2020; Vicario et al., 2020), leading to an increase in research on neuropsychological correlates of a number of chronic illnesses including cardiovascular disease (Eikeseth et al., 2020), diabetes mellitus (Martino et al., 2019a), bone health (Catalano et al., 2018; Fiegl et al., 2019; Kelly et al., 2019, 2020; Lauriola et al., 2019; Williams et al., 2020), fibromyalgia (Veltri et al., 2012; Palagini et al., 2016; Conversano et al., 2019; Marchi et al., 2019), as well as neuropsychological problems such as attention and hyperactivity deficit (Fabio et al., 2018; Di Giuseppe et al., 2020c) and post-traumatic stress disorder (Carmassi et al., 2014, 2018; Settineri et al., 2018; Conversano et al., 2020a; Merlo et al., 2020; Orrù et al., 2020). A number of recent studies have demonstrated that personality traits and implicit emotion regulation are associated with development, progression, recurrence, and severity of chronic illness (Koole and Rothermund, 2011; Ciuluvica et al., 2019; Settineri et al., 2019; Rymarczyk et al., 2020). For instance, the adaptiveness of defense mechanisms determines greater quality of life, adherence to treatment, and improved survival rates in cancer patients (Porcerelli et al., 2017; Zimmerman et al., 2019), which suggests the need for the systematic assessment of defensive functioning in chronic diseases (Di Giuseppe et al., 2020b). Adverse childhood experiences are also risk factors for metabolic alterations and obesity (Pervanidou and Chrousos, 2012; Davis et al., 2014). In particular, research in clinical psychology demonstrates high comorbidity between cardio-metabolic diseases and major depressive disorder (MDD). The occurrence of stressful life events (SLEs) appears to be related to cardio-metabolic complications and comorbidities, as they directly affect life stress and compensatory behaviors (Rich-Edwards et al., 2012; Kessler and Bromet, 2013; Kesebir, 2014; Rock et al., 2014). Furthermore, the impact of traumatic events on well-being is associated with the nature, timing, duration, and course of the SLE (Phifer and Norris, 1989; Fisher et al., 2010). Adults who experienced their most distressing trauma in childhood exhibited more severe symptoms of PTSD and lower subjective happiness as compared to adults who experienced it in a later stage of development (Ogle et al., 2013). Research has demonstrated that higher serum triglyceride and lower HDL-cholesterol concentrations can be observed in depressed patients with SLEs as compared to depressed patients without SLEs (Péterfalvi et al., 2019). Moreover, high LDLC and low serum levels of HDL-C were found to be associated with physical and sexual abuse, whereas raised TG and lower HDL-C were found to be associated with childhood neglect and emotional abuse (Li et al., 2019). Cardio-metabolic diseases are also associated with poor performance and cognitive dysfunction in memory, attention, visuo-spatial

abilities, and executive functions (Yaffe et al., 2009; Yates et al., 2012; Olson et al., 2017; Guicciardi et al., 2019; Wooten et al., 2019). Such a significant corpus of research has inspired reflection on how personality traits, defined as individual differences in characteristic patterns of thinking, feeling, and behaving (American Psychiatric Association, 2013), may affect the physical and psychological conditions of chronic patients.

Psychodynamic research has highlighted the role of personality in the development and progression of psychopathological and organic diseases (Price et al., 2001; Coughlin, 2011; Dell'Osso et al., 2012; Radziej et al., 2015; Boldrini et al., 2019; Catalano et al., 2019; Martino et al., 2020d). A number of studies have analyzed how personality characteristics may increase the risk of specific somatic diseases or the individual's general susceptibility to diseases (Friedman and Rosenman, 1959; Greer and Morris, 1975; Denollet et al., 1995; Horwood et al., 2015). Scholars have in recent years hypothesized that the occurrence of cancer is more frequent in individuals with cancer-prone personalities, also known as a Type C Personality (Eysenck, 1994; Watson et al., 1999; Lemogne et al., 2013). This hypothesis has been confirmed by research on defense mechanisms which has demonstrated that individuals who use mature defensive functioning, defined as the use of high-adaptive defensive strategies that lead the subject to the best adjustment and possible resolution of internal and external stressors, report higher physical and psychological functioning (Garssen, 2004; Paika et al., 2010; Petric et al., 2011; Perry et al., 2015; Di Giuseppe et al., 2019). Conversely, maladaptive defense style, defined as a combination of immature defensive strategies activated to keep the individual unaware of experiencing unmanageable feelings, desires, and thoughts, was shown to predict sleep disturbance, worse clinical conditions, and lower survival rates in cancer patients (Beresford et al., 2006; Hyphantis et al., 2011, 2013a,b; Hyphantis et al., 2016; Conversano et al., 2020c). In particular, the high use of repression leads to impairment of endocrine and immune functions and is common in patients with shorter disease-free intervals, shorter survival, and a more unfavorable cancer staging at endpoint (Bahnson and Bahnson, 1966; Kreitler et al., 1993; Weihs et al., 2000; Giese-Davis, 2008; Boscarino and Figley, 2009).

One aspect of personality commonly studied in patients with chronic diseases is alexithymia, which is defined as the inability to distinguish between emotions, thoughts, and physiological responses to stimuli. Alexithymia has been found to be associated with several medical conditions (Lumley et al., 2005; Willemsen et al., 2008; Honkalampi et al., 2010; Pouwer et al., 2010; Tolmunen et al., 2011; Mazaheri et al., 2012; Sapozhnikova et al., 2012; Shinkov et al., 2018). Alexithymia is associated with hyperarousal, physical symptoms, and unhealthy compulsive behaviors. Moreover, psychological treatments have poor outcomes in alexithymic patients, posing the question as to whether alexithymia can be improved through treatment (Lumley et al., 2007). Recent studies have found that alexithymic patients ranged from 25 to 50% among patients with Type 2 Diabetes Mellitus (Martino et al., 2020c) whereas this was not observed in patients with Inflammatory Bowel Disease (Martino et al., 2020b). This association between alexithymia and metabolic control was suggested by the negative correlation with HbA1c values. Since HbA1c reflects the mean serum glucose levels over time, it may be speculated that alexithymia may more probably be identified in patients with uncontrolled diabetes. Conversely, the attempt to restore euglycemia, in particular in subjects with high HbA1c and high serum glucose levels, may expose patients to hypoglycemic risk. Thus, the contribution of hypoglycemia, usually a manifestation of inadequately controlled diabetes, may not be ruled out. However, the study by Martino et al. was focused on a homogeneous T2DM population taking metformin and at relatively low hypoglycemic risk. Furthermore, alexithymia was found to be associated with anxiety and depression, especially in patients with poor compliance and adherence, concurring in a worse clinical picture and course of chronic diseases (Leweke et al., 2012; Hintistan et al., 2013; Mnif et al., 2014; Stanton and Hoyt, 2017; Rosa et al., 2019; Martino et al., 2020a).

Among other factors which contribute both to the onset and to the course of chronic illness, stressful life events are involved in the pathogenesis of both psychological and organic diseases (McFarlane, 2010; Afari et al., 2014; Marazziti et al., 2015). In addition, suffering from a chronic medical condition is a stressful factor *per se* and its influence on individual psychological well-being has been widely documented (Alonzo, 2000; Chaturvedi et al., 2017). Research has found that depression and psychosocial stressors promote inflammation and oxidative/nitrosative stress, decreased immunosurveillance and dysfunctional activation of the autonomic nervous system and of the hypothalamic-pituitaryadrenal axis (Piccinni et al., 2012; Bartolato et al., 2017). Accordingly, recent studies of the general population have demonstrated clinical levels of psychological distress, post-traumatic symptoms and somatization in response to the stressful condition of quarantining (Di Giuseppe et al., 2020d; Prout et al., 2020), confirming the effect of stress on physical and psychological well-being. Moreover, sociodemographic characteristics further contribute to increase hyperarousal and distress, with young people and women showing higher a prevalence of anxiety, depression and post-traumatic stress symptoms (Brooks et al., 2020; Conversano et al., 2020b) as well as a higher risk of developing chronic diseases (Abad-Díez et al., 2014; Holzer et al., 2017; Di Giuseppe et al., 2020a).

Taking these findings together, we assume that psychological and organic issues are intercorrelated and a comprehensive understanding of chronic medical conditions should consider all aspects of the illness (Yoo and Ryff, 2019). Effective therapy should be tailored to the needs of the patient, as suggested by personalized medicine. This approach promotes earlier diagnoses, risk assessment, and optimal treatments in order to ensure better patient care and lower costs (Vogenberg et al., 2010; Zilcha-Mano, 2020). In this perspective, psychotherapeutic interventions should be considered as an essential part of the treatment, since they are effective in reducing symptoms of psychological distress that, in turn, may affect disease progression and mortality (Lingiardi et al., 2010; Barrera and Spiegel, 2014; Salvatore et al., 2015; Gelo and Salvatore,

2016; Tanzilli et al., 2018; Perry et al., 2020; Yonatan-Leus et al., 2020). As suggested by Fonagy, we should use "*the opportunities provided by bioscience and computational psychiatry to creatively explore and assess the value of protocol-directed combinations of specific treatment components to address the key problems of individual patients*" (Fonagy, 2015).

AUTHOR CONTRIBUTIONS

CC and MD contributed in equal part to the development, conceptualization, literature review, and writing of the manuscript. All authors contributed to the article and approved the submitted version.

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OPINION
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Interventions to Promote the Quality of Life and Psychological Well-being in Chronic and Developmental Psychopathologies

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Keywords: quality of life, psychological well-being, developmental psychopathologies, interventions, prevention

Many studies have highlighted the role that the quality of life (QoL) plays for the individual's mental and physical well-being, preventing the onset of psychopathologies and chronic diseases (Marchini et al., 2018; Conversano, 2019; Martino et al., 2019, 2020a,b,c; Yoo and Ryff, 2019), which certainly have a serious impact on the general functioning of each individual. In fact, chronic diseases are frequently associated with psychopathologies, as they affect the cognitive, emotional and relational functioning, in all life contexts (Ingram and South, 2020; Lenzo et al., 2020; Marchini et al., 2020; Martino et al., 2020b; Vicario et al., 2020; Wang et al., 2020), also regardless the age.

This concept challenges psychologists to collaborate with other health professionals in order to structure interventions aimed at ensuring the better quality of life for the individual with different disabling diseases, since the early stages of the life cycle. In this regard, studies concerning children and adolescents with neurodevelopmental disorders highlight how it is necessary to promote learning, inclusion and consequently well-being in school and family environment. For instance, missing the adequate psychological support, children with oppositional defiant disorder (ODD) and attention deficit hyperactivity disorder (ADHD) can develop emotional disturbances, conduct disorders, and antisocial personality disorder in adulthood (Chen et al., 2020; Di Giuseppe et al., 2020). These psychopathological conditions are frequently associated with management difficulties of parents, who, in turn, risk to develop psychological symptoms and psychopathologies, such as anxiety and depression (Manti et al., 2019). Moreover, further difficulties in managing occur in school context, due to dysfunctional children behavior (Albertova, 2020; Han et al., 2020). Therefore, it is needed to structure parent and teacher training aimed at managing the disadaptive patterns, as well as reducing the oppositional, hyperactive and inattentive behaviors which characterize these specific disorders.

Psychological signs and symptoms are also associated to Specific Learning Disorder (SLD), negatively affecting their functioning and academic and social adaptation. Scientific evidences highlighted children with SLD have internalization problems, as anxiety and depression and externalization problems, as anger and aggressive behavior (Ryan, 2006; Mogentale and Chiesa, 2009; Ghisi et al., 2016; Mammarella et al., 2016; Sorrenti et al., 2019). If timely interventions are missing, internalization and externalization issues can evolve over time, eventually leading to psychosocial maladjustment. Instead, it is known low self-esteem, academic failure, school phobia, school refusal, school dropout, and absenteeism may be found among students with SLD (Venkatesan, 2017; Filippello et al., 2020b). These studies underline the importance of structured early interventions aimed at developing and enhancing learning strategies, such as metacognitive ones (Zumbrunn and Bruning, 2013; Filippello et al., 2016b), useful to promote learning and scholastic well-being. In fact, school is one of the main contexts in which it is necessary to promote the psychological well-being of all students, with particular regard to those with special educational needs (SEN). Indeed, they are more vulnerable, at risk of school failure and they could develop psychological illnesses in comparison with typically developing peers.

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Unfortunately, many students have internalizing problems that are not adequately addressed with psycho-educational interventions with the consequence that, getting worse, these problems can evolve into more serious and disabling psychopathologies, such as depression. Many researches highlighted several individual variables (e.g., dispositional optimism, personality, positive or negative affectivity, adaptive or dysfunctional explanatory style, emotional intelligence, frustration tolerance, adaptive, or maladaptive perfectionism) which play an important role in academic success, influencing the student's sense of self-efficacy, academic engagement, and psychological well-being (Saklofske et al., 2012; Filippello et al., 2016a, 2018a,b; Steinmayr et al., 2016; Damian et al., 2017). These studies also showed that if a negative circle exist between dysfunctional individual variables (e.g., pessimistic explanatory style, frustration intolerance, or maladaptive perfectionism) and school failure, the student can experience a sense of helplessness and, in the most serious cases, depression. Furthermore, these dispositional variables are often associated with contextual variables, such as relationships with parents and teachers. If these relationships are positive and supportive of the students' needs, there play a protective role against the development of psychopathologies; if not, being negative, they hinder the needs of adolescents, predicting psychological illness, school and social maladjustment, persisting over time (Wang, 2012; Haerens et al., 2015; Diaferia et al., 2018; Filippello et al., 2019a,b, 2020a,b; Buzzai et al., 2020). Finally, due to the chronic disorder and the severity of symptoms, psychological interventions could not be enough, and pharmacological treatments should be performed to promote QoL and psychological well-being.

In light of the above, effective interdisciplinary approach and collaboration between Psychology and Medicine are necessary, in order to better cure individuals suffering from chronic diseases and psychopathological disorders, in different contexts and lifelong, from childhood and adolescence. Thus, it is needed to timely identify specific psychological signs and symptoms, at early stages of life. A preventive perspective could significantly promote QoL and well-being with specific regards to developmental psychopathologies.

AUTHOR CONTRIBUTIONS

LS conceived the idea and made a significant contribution by drafting the manuscript. PF critically revised the manuscript and approved the final version to be published. All authors contributed to the article and approved the submitted version.

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The Psychodynamic Approach During COVID-19 Emotional Crisis

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The psychodynamic approach views human behavior from the standpoint of unconscious motives that influence personality functioning. In contrast with a nosological approach, the emphasis is on tracing behavior to its origins, fostering a deeper understanding of what is "behind" the overt signs and symptoms of disorder (Vaillant, 1977, 1992; Kernberg, 1988; Gabbard, 2014; Sartori et al., 2017; Mazza et al., 2019). From the early stage of development, the individual experiences life in peculiar ways that will progressively determine one's identity, including attitudes, coping strategies, cognitive processes, and relational dynamics (Cramer, 2007; Fonagy et al., 2008; Di Giuseppe et al., 2019b; Rosa et al., 2019; Giovanardi et al., 2020). Psychodynamic theories have offered a remarkable contribution to the study of unconscious processes connected with physical and mental distress. This approach has helped scholars in understanding the link between body and mind, detecting cyclical relational patterns, meaning individuals' behaviors and treating psychopathologies from an emotion-focused perspective (Bornstein, 2005; Bateman and Fonagy, 2012; Luyten and Blatt, 2015; Salvatore et al., 2015; Hilsenroth et al., 2018; McCarthy et al., 2019; Salvatore, 2019).

The impact of a dynamic approach in psychotherapy is largely documented (Midgley et al., 2009; Perry and Bond, 2012; Hilsenroth and Pitman, 2019; Lo Coco et al., 2019a; Gelo et al., 2020; Gennaro et al., 2020). Process-outcome research has highlighted the effectiveness of dynamic psychotherapy in treating various mental disorder such as depression (Meystre et al., 2017; Starrs and Perry, 2018; Perry et al., 2020), anxiety (Maffei et al., 1995; Babl et al., 2019; Solomonov et al., 2019) eating disorders (Gelo et al., 2015; Lo Coco et al., 2021), pathologic addictions (Terrone et al., 2018; Frisone et al., 2020; Lo Coco et al., 2020; Giordano et al., 2021), psychotic traits (Boldrini et al., 2019, 2020), externalizing problems (Prout et al., 2018a; Hoffman and Prout, 2020), and personality disfunction (Lingiardi and Giovanardi, 2017; Goldman et al., 2018; Aafjes-van Doorn et al., 2019; Kramer, 2019; Di Giuseppe et al., 2020b; Solomonov et al., 2020). The role of therapeutic alliance as mediator on outcomes in psychotherapy has been demonstrated in several studies highlighting the need for an in-depth investigation of patient-therapist communicative exchange (Lingiardi et al., 2010; Perry, 2014; Bhatia et al., 2017; Salvatore et al., 2017; Rocco et al., 2018; Tanzilli et al., 2018; Lo Coco et al., 2019b; Leibovich et al., 2020; Zilcha-Mano et al., 2020).

THE PSYCHODYNAMIC APPROACH AGAINST COVID-RELATED PSYCHOLOGICAL CONSEQUENCES

The health emergency we are experiencing due to COVID-19 has strongly influenced not only physical health but also the mental health of the general population as well as collective behavior (Gray et al., 2020; Orrù et al., 2020b; Lenzo et al., 2021). The understanding of mental health consequences must consider individual emotional responses associated with the ongoing stressful experience of the COVID-19 pandemic (Di Giuseppe et al., 2020a; Venuleo et al., 2020). Negative

emotions such as fear, anger, frustration and significant economic worries are associated with higher levels of anxiety, depression, sleep disturbances, maladaptive behaviors, and psychosomatic symptoms (Conversano et al., 2020b; Franceschini et al., 2020; Parola et al., 2020). As expected, the severity of clinical conditions is observed to be higher in vulnerable groups such as children, the elderly, psychiatric patients, and front-line workers (Aafjes-van Doorn et al., 2020b; Elbay et al., 2020; Elkholy et al., 2020; Merlo et al., 2020; Shen et al., 2020; Singh et al., 2020; Orrù et al., 2021). Research has demonstrated that emotion regulation plays a key role in stress management and adaptation helping the individual to cope with discharged feelings and thoughts related to the COVID-19 crisis, communication of the final stage of the individual's life (Iasevoli et al., 2012) and, therefore, protecting them from developing clinical levels of psychological distress (Di Giuseppe et al., 2020e; Prout et al., 2020; Walker and McCabe, 2021). The role of dynamic psychotherapy is essential in moderating people's emotional reactions, although its implementation requires the adjustment of therapeutic strategies enhancing adaptation and resilience (Aafjes-van Doorn et al., 2020a; Békés et al., 2020). From this perspective, it is imperative to improve public awareness and establish adequate procedures and prompt responses of intervention.

Due to uncertainty surrounding COVID-19, collective distress and individual suffering, the psychodynamic approach may be able to consistently identify and manage stressful life-event dynamics (Afari et al., 2014; Di Giuseppe et al., 2019a) as well as fostering emotional regulation in order to prevent possible relevant factors involved in the pathogenesis of both psychological and psychosomatic syndromes (Lenzo et al., 2020; Martino et al., 2020a,b; Conversano and Di Giuseppe, 2021; Sardella et al., 2021). This is of particular relevance at present with many experiencing grief and sorrow for the loss of a family member, a reduction of freedom, changes in daily routines and fears associated with uncertainty and the intolerance of uncertainty (Conversano et al., 2020a; Orrù et al., 2020a). In response to these stressors, the individual activates unconscious defense mechanisms, psychological strategies that help in reducing the anxiety associated with the awareness of internal conflicts and externally-charged situations (Perry, 1990; American Psychiatric Association, 2013). Since defense mechanisms are hierarchically organized and own specific psychological functions, they may cause a wide number of negative consequences as well as playing a significant role as protective factors against psychological distress and psychopathological symptoms caused by the COVID-19 outbreak (Marazziti et al., 2020). The use of high-adaptive defense mechanisms promotes increased awareness of one owns feelings related to difficult life experiences and leads to better adjustment and resilience, whereas the use of immature defenses protects the self from painful feelings and thoughts at the cost of developing maladaptive affective, cognitive and relational disfunctions (Di Giuseppe et al., 2014; Perry et al., 2019). Recent studies demonstrate that specific therapeutic intervention may increase the overall defensive maturity and improve psychological well-being and adjustment (Hoffman et al., 2016; Prout et al., 2018b, 2019; Di Giuseppe et al., 2020d).

CONCLUSIONS

In this opinion article the relevance of the implementing psychodynamic approach in the prevention of individuals' mental health during the ongoing COVID-19 crisis has been highlighted. In accordance with Marčinko et al. (2020), the inclusion of psychodynamic interventions within the public mental health emergency system is recommended, considered as an effective strategy in reinforcing the individual's well-being both during and after the COVID-19 pandemic crisis. The application of specific therapeutic interventions derived from the psychodynamic approach can enhance emotion regulation and adaptive responses as the COVID-19 pandemic progresses.

Understanding how the ongoing pandemic is influencing human reactions to such a stressful event is essential for developing *ad hoc* effective interventions. The systematic assessment of unconscious psychological aspects of personality should be promoted for the early detection of vulnerable individuals and for improving research and clinical practice toward a personalized therapeutic approach (Lingiardi and McWilliams, 2015; Lingiardi et al., 2015; Tanzilli et al., 2016; Barber and Solomonov, 2019; Talia et al., 2019; Di Giuseppe et al., 2020c; Zilcha-Mano and Ramseyer, 2020).

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The author confirms being the sole contributor to this work and approves it for publication.

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