Assessing and enhancing resilience to depression in people with long term medical conditions in the era of the current Greek social and financial crisis

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Introduction

Evidence supporting the association of economic insecurity with both psychological distress and health services use is strong, as is the evidence supporting the association of economic insecurity with major depressive disorder and suicide (1). Recent data from 29 European countries suggest a strong correlation between suicide rates and economic indices in men but only a correlation with unemployment in women (2). Meta-analyses of longitudinal studies concluded that unemployment is not only correlated to psychological distress and depression but is also a cause of it (3). Economic crisis variably affects specific vulnerable groups, with women being probably more exposed to the consequences of a crisis, although official unemployment rates are usually higher for men, even though the rate of job loss is usually higher for women (4).

Conducting a nationwide prospective telephone survey in Greece, Economou et al (5) found that the one-month prevalence of major depressive disorder (MDD) increased from 3.3% in 2008 to 8.2% in 2011, and a significant association was identified between MDD and economic hardship. Preliminary data suggest an increase in suicides in Greece during the current crisis (6). There are signs that health outcomes have worsened, especially in vulnerable groups (7), and a recent systematic review showed that this trend was greater in patients with LTCs (8). Preliminary findings of our research team showed a link between greater perceived impact of the current recession and MDD and suicidality in patients with LTCs seeking urgent care in our hospital's Accident and Emergency Department (AED) (9,10).

Previous studies of our research team (11-17) have shown that a quarter of all patients with LTCs have co-existing anxiety and depression which are associated with increased health service utilisation (18,19) and poorer health outcomes (20). We have also shown that the prevalence of MDD in Greek patients with rheumatologic disorders attending a follow-up clinic is estimated at 25.4% (11), while the prevalence of MDD in patients with LTCs attending our AED was 28.0% [16]. These findings indicate that patients with LTCs tend to be vulnerable to MDD, but whether this vulnerability and its association with the current crisis vary across subgroups of patients remains to be established.

Patients with LTCs and associated psychological problems have a range of unmet needs. In diabetes, depression is associated with more diabetes-related complications, impaired physical and mental health status and more emergency

department visits (21). We have previously found that several psychological parameters are associated with delayed engagement to treatment in diabetes (22) and that depression is strongly independently associated with more severe self-reported dyspnoea in COPD (23). Frequent scheduled care is associated with marked worry about the illness, fears that treatment will be ineffective and impaired coping (24). Our recent findings have also shown that illness perceptions of patients with LTCs are associated with frequent unscheduled care (25) and qualitative studies have demonstrated overwhelming anxiety at times of crisis leading to use of unscheduled care (26). A multivariable model is required to address the specific crisis-linked factors associated with the development of MDD in this patient group and to identify the most vulnerable to the rising social and income inequalities patients. A multimodal intervention targeting risk factors and enhancing resilience to MDD is also warranted to meet the patients' unmet needs, if we are to maintain and improve their health status and well-being during the current crisis in Greece.

A number of factors have been found to increase the risk for MDD or to enhance resilience to MDD and high consensus indicates that vulnerability to depression has been linked to the interaction among genetic predisposition, stressful life events and psychosocial parameters including personality traits (27-29). Convergent evidence poses the contributory role of genes in MDD but their mechanism of action has not yet clearly defined (29-32). Our previous findings have shown that gene polymorphisms combined with personality traits act as risk factors to the development of mental illness (33,34); inclusion of non-genetic variables and their link to the genetic background is considered fundamental in the study of mental disorder development, including MDD.

A great amount of clinical and preclinical evidence have shown that serotonergic (5-HT) neurotransmission, hypothalamico-adrenal axis (HPA) function and neurotrophins or heat shock proteins (HSPs), dedicated to housekeeping genes and stress-induced cellular activities, are implicated in regulation of mood, reactivity to psychological stress, self-control, motivation, drive, and cognitive performance (28,31,35-37). Genetic studies have hypothesized that a proportion of the risk of MDD is due to polymorphisms within genes related to the 5-HT neurotransmission, the HPA function and BDNF or HSPs expression (38,39).

On the other hand, a number of psychosocial and personality factors are considered to promote resilience to or increase the risk for MDD, including positive

emotions and active coping style, humour and optimism, cognitive flexibility and events with positive meaning (40). People and elderly patients who deal with religious activities and spirituality have more positive attitude towards illness and fewer depressive symptoms (41). Enhanced social support has been also associated with low levels of depression and stress, especially in patients with LTCs such as rheumatoid arthritis, cardiac illness, or cancer and comorbid depression (40). Lower socio-economic status (42), female sex (43), ceasing to cohabit with a partner (42), childhood trauma (44) and alcohol use/abuse (45) have been also associated with increased risk for MDD. Moreover, our previous research showed that adverse illness perceptions are also associated with depression and health outcomes in medical illness (17,46,47), and that the role of the patients' coping with stressors capacities and sense of coherence (SOC) should not be underestimated with regard to its contribution to depression development/alleviation (48-50).

No studies, however, have investigated which resilience/risk factors are of particular importance during a social and financial crisis and whether a biological and/or psychosocial element acts as mediator or moderator in MDD development/alleviation in high-risk populations such as people with LTCs with medium (routine care) or high (urgent care) levels of illness-related stress in a high-risk environment, such as the current Greek recession. Therefore, we plan to investigate a set of polymorphisms, and to test their interactions with psychosocial factors in promoting or preventing MDD development during the current Greek recession in the above mentioned samples.

The aim of the present study was to develop psychosocial strategies to enhance resilience to depression in most affected by the current Greek social and financial crisis vulnerable patients with three long term medical conditions. Our objectives were (a) to derive estimates of the prevalence of Major Depressive Disorder (MDD) and its predictors in patients with diabetes, rheumatologic diseases, and chronic obstructive pulmonary disease (COPD) as well as in alleged healthy participants; (b) to develop a ‘clinical prediction rule’ that will identify patients with long term conditions (LTCs) who are vulnerable to the current Greek crisis with respect to MDD development; (c) to identify factors that promote resilience to MDD; and (d) to develop a low-intensity intervention which will enhance resilience and prevent MDD in the era of the current recession.

Methods

Study design and participants

Data were collected during the study "Assessing and enhancing resilience to depression in people with long term medical conditions in the era of the current Greek social and financial crisis" and its main objective is to develop psychosocial strategies to enhance resilience to depression in vulnerable patients with LTCs facing the current Greek social and financial crisis, through a program of applied clinical research.

Baseline study

A total number of 505 subjects participated in the study. The sample comprised 376 patients with LTCs and 129 individuals without LTCs. The patient sample comprised patients with at least one of three LTCs: type-II diabetes mellitus (DM), rheumatological disorders (RD) and chronic pulmonary obstructive disease (COPD) who were seeking unscheduled or urgent care at the ED of the University Hospital of Ioannina (N=74) or were attending routine care in the respective follow-up specialty clinic (N=302) during a six-month period (9/2015-3/2016). Exclusion criteria were: inability to read and write Greek, active psychotic, intoxicated or confused or too severely unwell physically. Of the 116 patients in the ED who were approached, 86 were eligible and 74 agreed to participate (response rate 86.1%); 33 with DM only, 5 with RD only, 22 with COPD only and 14 with a combination of conditions. Of the 360 patients in routine care who were approached, 350 were eligible and 302 agreed to participate (response rate 86.3%); 88 with DM only, 172 with RD only, 7 with COPD only, and 35 with a combination of conditions. People without LTCs recruited from hospital staff. Healthcare workers in all hospital's departments and clinical Units were invited to participate. Exclusion criterion was a self-reported LTC (i.e. DM, RD or COPD). Two hundred and twenty potential participants were approached, 200 were eligible and 129 agreed to participate (response rate 64.5%). No statistically significant differences were found in age, sex, education and marital status between participants and non-participants across all samples.

Researchers were in the hospital from 8.00 a.m. to 4.00 p.m. every day and participants were recruited on a consecutive basis during this time frame. Inclusion criteria were age 18 or more and, for patients, a diagnosis of DM, RD or COPD confirmed by the treating clinician. Sampling was undertaken by three researchers,

trained psychologists (EN,VP,DP). The interviewers had at least 4 years of experience in diagnostic and clinical work in the Department of Psychiatry of the University of Ioannina and have also participated in courses on the administration of diagnostic instruments and screens. All patients with DM, RD or COPD attending the ED or a follow-up clinic during the sampling period were considered for recruitment. Eligible participants were approached by the researchers, and consenting participants were subsequently interviewed. The interviewers were blind to scores of the self-report questionnaires, which were administered the same day. All the procedures followed were in accordance with the World Medical Association Helsinki Declaration. The study was approved by the hospital's ethics committee (617/17–09-2015). Signed informed consent was obtained from all participants.

DNA isolation

Blood samples were obtained from 446 participants; 318 patients with at least one of three LTCs: rheumatological disorders (N=167), type-II diabetes mellitus (N=85), chronic pulmonary obstructive disease (N=25), or a combination of two conditions (N=41) attending specialty clinics or the emergency department (blood samples obtained rate: 86.2%) and 128 people without LTCs recruited from the hospital staff (blood samples obtained rate: 64.5%). DNA was isolated from whole blood samples with the use of the QuickGene DNA whole blood kit (DB-S, Kurabo, Osaka, Japan) and the QuickGene-810 automated nucleic acid extraction system (FUJIFILM, Singapore). DNA was amplified with polymerase chain reaction (PCR), using the KAPA Taq DNA polymerase (KK1015, KAPA BIOSYSTEMS, Boston, US) according to instructions, with the forward primer GGCGTTGCCGCTCTGAATGC and the reverse primer GAGGGACTGAGCCTGGACAACCAC. The PCR products were separated by electrophoresis in a 3% agarose gel prepared with GelRed nucleic acid gel stain (41003, Biotium, Freemont, CA, USA). Two allele variants were identified based on PCR fragment sizes: long (L, 530bp) and short (S, 426 bp).

Prospective study – Six-month follow-up

From the initial total number of 505 subjects participated in the baseline assessment, 378 participated in the six-month follow-up (participation rate: 74.9%). Three patients were died (0.6%), 10 (2.0%) refused to participate in follow-up and 114 (22.6%) were not found, as they were residents in several distant places in Greece and they were visiting the hospital sporadically. From the follow-up sample of 378 participants,

blood samples had been obtained from 339 subjects (blood samples obtained rate: 89.7%), and this sample was the final sample in the present study, 25 (7.4%) patients attending the emergency department, 204 (60.2%) attending specialty clinics, and 110 (32.4%) participants without LTCs. Sixty-three patients (18.6%) had DM only, 121 (35.7%) had RD only, 19 (5.6%) had COPD only and 10 (4.4%) a combination of them.

Low-intensity intervention

The purpose of this part of the programme was to provide an evidence-based guidance for developing a credible, practical, low intensity intervention to be used in conjunction with the "clinical prediction rule". In other words, what should happen when a patient is identified by the clinical prediction rule, as being potentially depressed. Due to the very limited available time, our intention was to provide guidance to future research to develop a preventative intervention. The intervention was two-fold:

(a) A qualitative study was carried out aiming to provide a detailed and practical understanding of who is resilient to or at risk for MDD in relation to the current social and financial crisis, what they experience, and what are the major therapeutic factors for enhancing resilient and reducing depressive symptomatology. For this, two psychologists (VP and EN) interviewed at home 10 at risk for MDD individuals using the criteria and procedures derived from the baseline assessment. We also selected 5 individuals with low MDD risk for interview at home about how they manage the kinds of factors that drive to psychological distress, focusing on factors relevant to the current social and financial crisis. For individuals at risk, interviews aimed to identify their own reasons for their condition by prompting them to describe their illness-perceptions and their experience of health care in the era of current recession. To avoid generalized or idealized accounts, interviews focused on specific instances where a coping strategy was sought, considered or avoided.

(b) All patients diagnosed either with MDD or with any other psychiatric condition were re-approached by the psychologists-researchers or were referred to the outpatient department of psychiatry and were offered appropriate treatment, i.e., antidepressant/anxiolytic medications and/or psychotherapy, as indicated. In addition, all patients with LTCs were administered relative to their underlying

medical condition informative material derived from our previous research (http://abreviate.project.uoi.gr/index.php/el/2015-02-28-16-51-43/astheneis-frontistes) and they have been advised to visit the relevant website (http://abreviate.project.uoi.gr/index.php/el/) for gaining additional information regarding their medical illness and associated mental complications and/or comorbidities. This material aimed to increase the patients' awareness about their conditions providing information to enhance self-management of the illness and/or lifestyle changes including diet and exercise. Finally, the "doctor's card" (http://abreviate.project.uoi.gr/index.php/el/2015-02-28-16-51-43/astheneis-frontistes-2/64-2015-03-22-13-27-24) which was produced in our previous research was administered to all medical staff that came in touch with the researchers, in an effort to increase their potential to early diagnose and treat the common mental disorders (depression, anxiety, suicidal risk, alcohol and substance abuse and severe cognitive decline).

Measures and study instruments

Demographic variables including age, sex, marital status, residence, employment status and occupation were collected. History of mental illness was also recorded and, for patients with LTCs, clinical features, disease severity indices and laboratory data were obtained from patients' records. The current use of any agent including antidepressants was also recorded. Coexisting medical diseases were scored using the Charlson comorbidity scale (51). Parameters regarding the impact of the current Greek social and financial crisis were also recorded including percentage of income reduction during the last two years, unemployment rates and unemployment due to personel cuts. Participants were also asked to define the perceived degree of the negative impact of the crisis upon their social and financial status on a 1-9 Likert-type scale (*not at all* to *very much*).

Baseline assessments

Mental diagnoses were confirmed using the Greek version 5.0.0 of the Mini International Neuropsychiatric Interview (MINI) (52). The MINI is a structured psychiatric interview that ascertains the diagnosis of mental disorders according to DSM-IV or ICD-10 criteria (53). It focuses mainly on current diagnosis and contains 120 questions for screening 17 axis I disorders. The MINI has been previously used in studies with Greek medical patients (54,55).

Resilience was assessed using the Greek version of the 14-item Wagnild and Young Resilience Scale-14 (RS-14) (56) after licensing. RS-14 is 7-point Likert-type scale and scores range from 1 (strongly disagree) to 7 (strongly agree); sum score range from 14 to 98. Higher scores indicate stronger resilience. Scores greater than 90 indicate high resilience, 82-90 moderately high, 65-81 moderately low to moderate, 64 to 57 low, and scores below than 56 indicate very low resilience (57). The psychometric properties of the scale have been extensively tested in a number of studies across several samples and languages and principal component analyses revealed a single-factor solution with Cronbach's alpha coefficients ranging from 0.72 to 0.94, supporting the internal consistency reliability of the RS-14 (58). The results of the present study showed that the Greek version of RS-14 may reliably assess resilience, while Cronbach's alpha for the RS-14 in the present study was 0.89 (59).

Sense of coherence was assessed using the Greek translation of the Antonovski's sense of coherence scale (60). The Sense of Coherence (SOC) Scale is a 29-item questionnaire based on Aaron Antonovsky's salutogenic theory, and it is considered to be a measure of the stable dispositional orientation of a person (61,62), and it is essentially a measure of an individual's capacity to cope with stress. Those having high SOC scores are likely to perceive stressors as predictable and comprehensible and to perceive the challenges of life as meaningful and worth making commitments for, and, in addition, they have confidence in their capacity to manage. Respondents are asked to select a response, on a seven-point semantic differential scale with two anchoring phrases. There are 11 comprehensibility, 10 manageability and 8 meaningfulness items. Thirteen of the items are formulated 'negatively' and have to be reversed in scoring, so that a high score always expresses a strong SOC (61).The psychometric properties of the scale have been extensively tested in a number of studies across several samples and languages with Cronbach's alpha coefficients ranging from 0.70 to 0.95, supporting the internal consistency reliability of the SOC (63). The results of the present study showed that the Greek version of SOC-29 may reliably assess SOC, while Cronbach's alpha for the SOC-29 in the present study was 0.90 (64).

Religious affiliations and levels of *religious participation* were obtained using the Duke University Religion Index (DUREL) (65). DUREL is a 5-item Likert-type scale measuring three dimensions of religiosity: organizational religious activity

(ORA), non-organizational religious activity (NORA) and intrinsic religiosity (IR), with scores ranging from 1 to 5 for IR and from 1 to 6 for ORA and NORA.

Religious coping was assessed with the Brief Religious Coping inventory (B-RCOPE). The B-RCOPE is comprised of 14 items distinguishing between Positive Religious Coping (PRC) and Negative Religious Coping (NRC) styles: 7 items reflect PRC and 7 items reflect NRC (66). The score of each item ranges from 1 ('not at all') to 4 ('a great deal'), and the total score ranges from 7 to 28 for each subscale; the higher the score, the stronger the PRC and NRC, respectively. PRC items rely on a secure relationship with God, whereas NRC items reflect religious struggle that grows out of a more tenuous relationship with God (67). Evidence indicates higher means and greater variance for the PRC than for the NRC subscales, and numerous studies support the validity and reliability of the B-RCOPE (68). The results of the present study indicated that the Greek-Orthodox B-RCOPE version may reliably assess religious coping, while Cronbach's alpha for the B-RCOPE in the present study was 0.96 for PRC and 0.92 for the NRC (69).

Illness perceptions were assessed using the Brief Illness Perception Questionnaire (B-IPQ) (70). The B-IPQ is a nine-item scale developed to assess the cognitive and emotional representations of illness using a single-item approach on a 0-10 scale to assess perceptions relevant to: *consequences* (how much does your illness affect your life?), *timeline* (how long do you think your illness will continue?), *personal control* (how much control do you feel you have over your illness?), *treatment control* (how much do you think your treatment can help your illness?), *identity* (how much do you experience symptoms from your illness?), *concern* (how concerned are you about your illness?), *emotions* (how much does your illness affect you emotionally?) and illness *comprehensibility* (how well do you feel you understand your illness?). The B-IPQ is a widely used instrument and a recent systematic review with meta-analysis showed that pooled correlations between illness perceptions and depression, anxiety, and quality of life were consistent with previous research and theory (71).

Outcomes

Depressive symptom severity was assessed using the validated Greek version of the Patient Health Questionnaire-9 (PHQ-9) (11,72). This instrument screens for DSM-IV major depressive disorder. The frequency of symptoms is rated over the past 2 weeks

on a 0–3 Likert-type scale; summed scores range from 0 to 27. Higher scores indicate more severe symptoms. The PHQ-9, at an optimum threshold of 10, has shown 81.2% sensitivity and 86.8% specificity in diagnosing depression among Greek medical patients (11). Cronbach's alpha for the PHQ-9 in this sample was 0.83.

Suicidal risk was assessed using the standardized Greek version of the Risk Assessment Suicidality Scale (RASS) (73). RASS is a brief 12 item self-report instrument of suicidal risk behaviours. It contains items relevant to intention, life, and history of suicide attempts, which are rated on a 0-3 Likert–type scale (not at all to very much) and the scores were transformed according to the suggestions of the standardization study for use within the Greek population (73). In patients with LTCs attending the ED, we have found that at an optimal cutpoint of 270 the scale had 81.3% sensitivity and 81.8% specificity, with a Cronbach's α of 0.80 (74). Higher scores indicate greater suicidal risk.

Health-related quality of life (HRQoL) was assessed using the 26-item validated Greek version of the World Health Organization Quality of Life Instrument, Short Form (WHOQOL-BREF) (75). It assesses six domains, overall HRQoL, General Health, Physical, Mental, Social Relations and Environment HRQoL. Each item is rated on a 5-point Likert scale and the scores are transformed on a scale from 0 to 100. Higher scores indicate better HRQoL.

Six-month follow-up assessments

The same interviewers interviewed the patients six months after the initial assessment. At that point the inventories measuring the main outcomes of the study (PHQ-9, RASS and WHOQOL-BREF) were administered.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (SPSS Inc., Chicago, IL, USA) for Windows. Summary statistics for all variables were calculated. Normality was tested by the Kolmogorov-Smirnov test (76). Chi-square analyses for categorical data and two-tailed t-tests for continuous data were carried out to assess the differences between groups of participants. Chi-square analyses were also performed to assess the differences in mental disorders between males and females as well as in genotype frequencies across samples and diagnosis of MDD.

To assess the factors associated with depressive symptom severity at baseline bivariate Pearson correlation analyses were performed separately for patients and controls, followed by multiple linear regression analyses with dependent variable the PHQ-9 score at baseline and independent variables all the variables of interest based on the study's hypotheses. Changes in outcomes (i.e. PHQ-9, RASS and WHOQOL-BREF) were assessed using paired sample t-tests. Finally, predictors of change in PHQ-9 scores between baseline and follow-up were assessed by performing two separately produced linear multiple regression analyses for patients and controls with dependent variable the change in PHQ-9 scores between baseline and follow-up and independent variables all the variables of interest based on the study's hypotheses.

Qualitative analysis was carried out by the three researchers, two psychologists and one psychiatrist. A thematic analysis procedure was used to categorise and recurring themes within and between transcripts. Themes were identified using an open-ended method and a preliminary coding frame was constructed using the interview schedules to structure the themes. Transcripts were analysed independently, then emerging themes were discussed until consensus was achieved. Each transcript was analysed individually and then in groups.

Results

Descriptive data and crisis parameters

Table 1 presents the participants' characteristics across the two samples. As shown in this Table, patients with LTCs were older and had received less education compared to participants without LTCs. In addition, the majority of patients (55.5%) were pensioned. Nineteen patients (8.3%) were unemployed, an additional number of 51 (26.8%) were unemployed due to ill health, while 12 patients had had lost their job due to the cuts attributed to the financial crisis. The mean percentage of income reduction during the last 2 years (2013-15) was 33.8% for the patient sample and 29.3% for the healthy participant sample. As for the perceived impact of the crisis, both groups reported similar perceived impact. Also, resilience levels were similar to both samples, but patients with LTCs presented lower levels of sense of coherence compared to people without LTCs (Table 1).

Prevalence of Major Depressive Disorder (MDD) and other mental disorders

As shown in Table 2, approximately half of the patients presented with mental illness of any kind, mostly MDD (23.6%). In addition, large proportions were diagnosed with Generalized Anxiety Disorder (GAD) (19.6%), whereas there were remarkable proportions identifying with suicidal risk (14.4%, mostly of low risk), dysthymia (7.4%), panic disorder (6.5%), and agoraphobia (4.8%). The respective proportions within the control sample (healthcare workers) were lower but still relatively high: 20.9% presented with any mental disorder and 10.9% with MDD.

As shown in Table 3, although there was a trend for more females to be presented with a diagnosis of a mental disorder, the differences failed to reach statistical significance, with the exception of suicidal risk, where significantly more females with LTCs were identified with suicidal risk compared with their male counterparts (p=0.015).

Frequencies of 5-HTTLPR genotypes and associated parameters

Genotype and allele frequencies (L: 0.58, S: 0.42) were in Hardy-Weinberg equilibrium ($\chi^2(1) = 0.78$, $p>0.05$) and in agreement with previous findings (77). There were no significant differences in genotype frequencies across age ($F_{[2,325]}=1.2$, p=0.30), marital status ($\chi^2(2)=0.79$, p=0.67), education ($\chi^2(6)=5.9$, p=0.42), other comorbidities ($F_{[2,307]}=0.24$, p=0.78) or across disease type ($\chi^2(12)=16.7$, p=0.16). There were also no significant differences in genotype frequencies across income reduction rates ($F_{[2,274]}=2.34$, p=0.09), perceived impact of the crisis ($F_{[2,328]}=0.44$, p=0.64), Resilience as measured with the RS-14 ($F_{[2,332]}=2.44$, p=0.09), sense of coherence as measured with the SOC-29 ($F_{[2,289]}=2.4$, p=0.09), or positive ($F_{[2,324]}=0.61$, p=0.54) or negative religious coping ($F_{[2,324]}=1.0$, p=0.37). Finally, within the patient sample, no significant differences were observed in genotype frequencies across illness perceptions (data available upon request).

As shown in Tables 4 and 5, there were also no significant differences in genotype frequencies across the two groups of participants or across a diagnosis of MDD.

Factors associated with depressive symptom severity at baseline

Univariable analyses showed that, in the participant without LTCs sample, the variables significantly associated with PHQ-9 scores at baseline were: education (r=-0.221, p=0.020), income reduction (marginally, r=0.204, p=0.088), resilience (r=-

0.210, p=0.027), sense of coherence (r=-0.555, p<0.001), and negative religious coping (r=-0.296, p=0.002). In the patients with LTCs sample, the significant correlates of PHQ-9 were age (r=-0.161, p=0.016), education (r=-0.191, p=0.004), the perceived impact of crisis (r=0.152, p=0.023), resilience (r=-0.358, p<0.001), sense of coherence (r=-0.638, p<0.001), positive religious coping (r=-0.163, p=0.016), negative religious coping (r=0.284, p<0.001), as well as most illness perceptions (consequences, r=0.344, p<0.001; personal control, r=-0.156, p=0.020; treatment control, r=-0.222, p=0.001; identity, r=0.449, p<0.001; illness concern, r=0.368, p<0.001, and comprehension, r=-0.147, p=0.027).

Multivariable analyses presented in Table 6 showed that in people without LTCs the variable most closely associated with depressive symptom severity at baseline was the sense of coherence, whereas education and positive religious coping may also play a role. Within the patient with LTCs sample, being S-carrier, lower sense of coherence, greater use of negative religious coping and higher identity perception of the illness were the variables most closely associated with depressive symptom severity at baseline.

Changes in outcomes between baseline and 6-month follow-up (low-intensity intervention indicators)

As shown in Table 7a, in the total sample, depressive symptom severity was significantly improved between baseline and follow-up (p<0.001). This improvement was evident in both samples (Tables 7b and 7c). Suicidal risk improved also greatly within the patient sample (p<0.001), and this was the case for all subscales of HRQoL in the patient sample (Table 7c). Finally, within the patient without LTCs sample, a worsening in social relations HRQoL was observed (p<0.001), while environment HRQoL was improved (p=0.019) (Table 7b).

Predictors of change in depressive symptom severity between baseline and follow-up

As shown in Table 8, within the participants without LTCs sample greater sense of coherence was most closely associated with improvement in depressive symptom severity (p=0.003), while not being an S-carrier showed a trend to marginally associated with depressive symptom improvement (p=0.058).

Within the patient sample, greater sense of coherence (p=0.013), lower perceptions regarding the consequences of the medical illness (p=0.009) and better perception of the identity of the illness (p=0.037) were the variables most closely

associated with improvement in depressive symptom severity between baseline and follow-up. Again, not being an S-carrier showed a trend to marginally associated with depressive symptom improvement (p=0.059).

Qualitative analysis

Key themes that emerged from the content analysis of the interviews suggested that the main risk factors for MDD in patients with LTCs were (1) the financial crisis, (2) the severity of underlying physical illness, and (3) the patient's social environment.

Financial crisis

Most depressed patients stated clearly that Greek financial crisis has greatly affected their psychological status:

> *"The income reduction in recent years has played an important role in my psychology",*
>
> *"Nowadays there is a financial insecurity and you can't feel happy when you have a long term condition in a country with financial crisis, so I feel more stressed and afraid for the future".*

On the other hand, patients without MDD reported that the financial crisis had little or no impact to their psychology

> "*Even though as a self- employed my income faced a significant reduction since 2014 I don't think that this can affect my psychological status".*

Severity of the physical illness

In total, most patients reported that the severity and inveteracy of their physical illness have substantial impact to their emotions, regardless of their mental health diagnosis:

> *"Sometimes I ask myself why all this has happened to me? And I have a bit of a cry; it's a very hard pill to swallow when you've been so active".*

With regard to the link between the severity of the physical illness and MDD, it is essential to mention that patients with rheumatologic diseases added to the qualitative results the contribution of pain as a significant risk factor for psychological distress:

> *"Aches and pains in the limbs and muscles and back and legs make you feel absolutely drained out and you can't focus, you can't think, and you can't feel optimistic for your everyday life".*

Moreover, one patient stated:

> "*I have so much pain in my joints; I am sick more than 12 years. Sometimes I weak up and I can't put my clothes and this makes me feel psychologically strained and useless".*

Social environment

The patients of the study who diagnosed with MDD reported that depression and distress are greater within a context of a low social support. Many patients are facing divorces, family losses, loneliness and difficulties in their family context and, as a result, they reported distress more often that those who receive emotional, informative and instrumental support by family and friends.

> " *…I have the disease many years so it is not only the severity of the disease that makes me feel sad, but also the difficulties that my family face . ... Not only my children's problems but also the relationship with my husband, as there is a distance and I don't have the support I need, as I come alone in the hospital for many years and I don't feel that he understands me".*

Another patient focused on his loneliness:

> *" I am alone every day; I work many hours and I don't feel I have time for social life as I have to be either at work or in travelling from Athens to Ioannina to be in the hospital for my treatment, so I feel there is not something that will change my bad mood when I am in pain".*

An interesting statement resulted from the content analysis reported from a small proportion of the participants was that the first announcement of the disease was linked to a significant life event, usually marriage, divorce, or pregnancy, mainly for patients with rheumatic diseases. For example, a patient with RA described a story about how the diagnosis was confirmed the day before his wedding.

Resilience

The interviews regarding the factors associated with resilience to depression revealed that the key themes emerging were relevant to: (1) Social Environment, (2) Relationship with the doctor, and (3) Financial security.

Social Environment

Supportive family and social environment were mentioned by the patients as important protective factors for depression development:

> *"The most important in my life is my family and my children. I excerpt power from my family and my two children, as they support me all these years with the disease"*
>
> *"The fact that my income reduced the last years didn't affect my psychological status because I have my family and I am happy that they are all healthy".*

Relationship with the doctor

In patients without depression, the relationship with their doctor seems to have an important role in enhancing resilience to depression:

> *"I have great confidence in my doctor and this gives me mental strength"*
> *"The doctor helps us a lot even when we are afraid; he explains to us everything and this can make you feel better"*

Financial security

The interview with the patients gave prominence to the socio-economic status as a significant factor for a "happier" life. A significant amount of patients stated that financial security and wealth contribute to their psychological well-being and increases individuals resilience to depression:

> *"... Travelling can make me feel better as in the past it was a hobby that I used to do often and now the money aren't enough for travelling or going out with friends and as a result after job I am alone"*
> *" ... Activities, travelling and maybe better financial situation could change depressive feelings"*

Discussion

1. Prevalence of Major Depressive Disorder and level of Resilience

Our first aim was the estimation of the prevalence of major depressive disorder and the level of resilience in Greek patients with diabetes, rheumatologic disorders and chronic obstructive pulmonary disease (COPD) attending a routine clinic or the ED in comparison with alleged healthy individuals. Our findings showed a high prevalence of major depressive disorder of 23.6% in the patients with LTCs sample, while remarkable proportions were diagnosed with GAD (19.6%), suicidal risk (14.4%), dysthymia (7.4%), panic disorder (6.5%), and agoraphobia (4.8%). The respective proportions within the control sample (healthcare workers) were lower but still relatively high: 20.9% presented with any mental disorder and 10.9% with major depressive disorder.

The prevalence of MDD and GAD was high among people with LTCs as anticipated (74), but we also found a high prevalence of MDD in the control sample. This prevalence of MDD in the control sample (hospital healthcare workers) is in line with the results of Economou et al. (78), who reported a 12.3% prevalence of depression for the general population in 2015. These authors reported that the prevalence of depression in the general population increased from 3.3% in 2008 to

8.2% in 2011 reaching the current levels of 12.3% in 2015 (78-80). We have also found a 6.8% prevalence of severe psychological distress using the GHQ-28 among healthcare workers of the same hospital in 2009 (81). Although the use of different instruments prevents a direct comparison between the studies, present findings and the results of the aforementioned studies indicate that depression rates are rising as the recession persists. The high prevalence of MDD found here among healthcare workers also raise intriguing questions regarding the extent of the effects of the financial crisis upon the health care systems. The adverse impact of the current recession upon the healthcare system has been previously mentioned (82,83), and professionals working in general hospitals face cutbacks in salaries up to 40%, as the present study confirms, in addition to an increased workload, impaired morale (84) and uncertainty provoked by the crisis.

Resilience levels as measured by the RS-14 were not different across the two samples and both patients with LTCs and people without LTCs presented similar levels of resilience. In general, a great proportion of the sample presented moderately low to moderate resilience levels (65-81), 11.3% presented low resilience levels (<64), 29.3% moderately high (82-90) and 18.2% high resilience levels (>90) (59).

Regarding the parameters of the current Greek crisis, participants of all three groups reported a substantial income reduction between 2013 and 2015. However, people with LTCs reported greater cuts compared to controls (33.8% vs. 29.3%, respectively, $p<0.001$). It should be mentioned, however, that the patients were older and mostly pensioned, and this finding reflects the greater cuts applied in pensions as the result of austerity measures.

2. Identification of the genetic profile and the psychosocial factors associated with major depressive disorder and resilience

Genotype and allele frequencies (L: 0.58, S: 0.42) were in Hardy-Weinberg equilibrium ($\chi^2(1) =0.78$, $p>0.05$) and in agreement with previous findings (77). There were no significant differences in genotype frequencies across age, marital status, education, other comorbidities or across disease type. There were also no significant differences in genotype frequencies across income reduction rates, perceived impact of the crisis, resilience levels, sense of coherence, or positive or negative religious coping. Also, within the patient sample, no significant differences were observed in genotype frequencies across illness perceptions. There were also no significant

differences in genotype frequencies across the two groups of participants or across a diagnosis of MDD. However, depressive symptom severity was associated with S-carriers (p=0.049) and improvement of depressive symptom severity was marginally associated also with S-carriers.

Our results confirm the few previous findings reporting that 5-HTTLPR, a polymorphism in the promoter region of *SLC6A4*, the gene that encodes for the serotonin transporter (5-HTT), could moderate the association between stress and depression (85), as we found this link only in the patient with LTCs (i.e. vulnerable to stress) sample. For example, in a study with an East Asian community sample of older people, the association between the number of somatic disorders and depression was significant in S/S homozygotes but not in heterozygotes or L/L homozygotes (86). Also, a recent meta-analysis found strong evidence for an association between the S allele and an increased risk of developing depression under stress in groups with specific medical conditions (85). On the other hand, in a population study, S-carriers with low social support had lower levels of resilience, less sense of coherence, and more depressive symptoms (87). Our study further supports the link between the S allele with psychological vulnerability, and as the study on the role of additional genetic factors such as monoamine oxidase A (MAOA), catechol-O-methyltransferase (COMT), HTR1A, 5-HT2A polymorphisms, genes of the HPA axis and neurotrophins and housekeeping genes and their respective polymorphisms brain derived neurotrophic factor (BDNF) and housekeeping HSP70 (A8) and HSP90 genes, are under preparation, a combined analysis may shed more light in the complex interplay between the substrate and the environment.

On the other hand, depressive symptom severity of patients with LTCs was associated with S-carrier group, younger age, less received education, greater perceived impact of the crisis, lower levels of resilience and sense of coherence, lower positive religious coping and greater adoption of negative religious coping. In addition, illness perceptions, namely consequences, personal control, treatment control, identity, illness concern, and comprehension, were also significantly associated with depressive symptoms in patients with LTCs. However, when all variables were taken into account, being S-carrier, lower sense of coherence, greater use of negative religious coping and higher identity perception of the illness were the variables most closely associated with depressive symptom severity.

In people without LTCs, depressive symptom severity was associated with lower education received, greater income reduction during the last two years, lower levels of resilience and sense of coherence and greater adoption of negative religious coping. When all variables were taken into account, however, only sense of coherence was the significant correlate of depressive symptom severity.

These findings indicate that the most important independent factors associated with depressive symptom severity are *sense of coherence* in both health and disease and a *genetic vulnerability* along with *illness perceptions* in patients with medical illness.

Sense of coherence is defined as a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence that:

I. The stimuli deriving from one's internal and external environments in the course of living are structured, predictable, and explicable;
II. The resources are available to one to meet the demands posed by these stimuli; and
III. These demands are challenges, worthy of investment and engagement [2]. It is a dispositional orientation rather than a personality trait/type or a coping strategy [2,4] and its importance to a person's mental and physical health has been widely recognized in a number of studies and excellent reviews.

In accordance with present findings, sense of coherence (SOC) has been found strongly related to perceived health, especially mental health; this relation was manifested regardless of age, sex, ethnicity, nationality, and study design, while SOC was able to predict health (88). SOC has been also found to have an impact on the quality of life; the stronger the SOC, the better the quality of life, and longitudinal studies confirm the predictive validity of the SOC for a good quality of life (89). Furthermore, a strong sense of coherence among older people was associated with better physical, social and mental health (90) and low SOC could be a marker of risk for high suicidality in the aftermath of a suicide attempt (91). Finally, studies provide support for the clinical relevance of SOC in cancer patients (92) with SOC having both a moderating and mediating effect on health (especially mental health and quality of life) in colorectal cancer patients, while preliminary data indicate that SOC may be an independent predictor of colorectal cancer patients survival (93).

It is widely accepted that patients' own views and beliefs about their condition can influence their way of responding both emotionally and physically to their illness (94). These views, frequently described as illness perceptions, represent patients' need

to make sense of and respond to their illness (95). Leventhal's self-regulation model is commonly used to explain peoples' psychological response to illness. This model involves a continuous feedback loop of three stages; illness representation, the adoption of coping responses, followed by appraisal of how successful the coping responses have been (95). In accordance to present findings, studies have shown that, in people with LTCs, illness perceptions are associated with psychological distress (96-98). Furthermore, studies within the primary care setting have shown that a strong illness identity (the number of symptoms attributed to the illness), a long timeline perspective (a belief that the illness will continue for a long period of time), and a belief in serious consequences of the illness are strong predictors of health care use (99).

Published data from the present study (59) have also shown that resilience is significantly correlated with mental illness: people with MDD, panic disorder or GAD presented lower resilience rates compared to those without a mental disorder; resilience was also negatively related to depressive symptom severity, but the addition of SOC rendered this association non-significant, indicating that SOC may be a stronger correlate of depression symptom severity than resilience.

The resilience approach in mental health research proposes a biopsychosocial model, including components relevant to biological predispositions, personal adaptive and maladaptive re-activities (e.g., coping behaviors), individual psychological development and social factors (100). In this realm, measures of resilience have been found strongly associated with mental health in both general population and physical illness (101-105). In line with present findings, all previous studies performed have also found sound negative correlations between RS-14 and depression (106-110).

3. Validity of the psychological instruments used in the present study

Published data derived from the present study support the use of the Greek versions of RS-14, SOC-29 and R_COPE for use within the Greek population. More specifically:

a. The Greek version of RS-14 showed a coherent one-dimensional factor structure with remarkable stability across the three samples. Cronbach's alphas were 0.88-0.91 across the three samples, being 0.89 for the entire sample. Furthermore, greater RS-14 scores were associated with better mental health, lower depressive symptom severity and suicidal risk (59).

b. The Greek version of SOC-29, when used as a whole, presented a coherent structure with remarkable stability in people with and without LTCs. Cronbach's alphas were 0.89 for patients with LTCs and 0.91 for people without LTCs, being 0.90 for the entire sample. Greater levels of SOC were associated with better mental health, lower depressive symptom severity and better quality of life. Furthermore, greater levels of SOC were associated with lower suicidal risk even after adjustment for depressive symptom severity (64).
c. The Greek version of B-RCOPE showed a coherent two-dimensional factor structure with remarkable stability across the three samples corresponding to the positive (PRC) and negative (NRC) religious coping dimensions. Cronbach's alphas were 0.91–0.96 and 0.77–0.92 for the PRC and NRC dimensions, respectively. Furthermore, NRC was associated with poorer mental health, greater depressive symptom severity and suicidality, and impaired HRQoL. In patients with LTCs, PRC correlated with lower perceived illness timeline, while NRC was associated with greater perceived illness consequences, lower perceived treatment control, greater illness concern, and lower illness comprehensibility (69).

4. A clinical prediction rule for identifying resilience factors for MDD

The formulation of a clinical prediction rule was based on the results of the analyses performed to assess the correlates of depressive symptom severity at baseline, the results of the analyses carried out to assess the predictors of improvement in depressive symptom severity between baseline and follow-up and the results of the qualitative study. In addition, mental correlates of crisis parameters were also taken into account.

The frame of the financial crisis seems to differentiate patients with LTCs from people without LTCs as well as depressed and non-depressed participants. Patients experienced greater financial cuts during the last two years, while the perceived impact of crisis was correlated with depressive symptom severity only in patient sample. Published data derived from the present study indicate also a moderator effect (according to Miles & Shevlin method [111]) of major depressive disorder in the relationship between the perceived impact of the crisis and suicidal risk in the patient group: the greater the perceived impact of the crisis the greater the suicidal risk only when major depressive disorder is present. This finding indicates

that, apart from the recognized relationship of mental illnesses with suicidal risk (112-114), the impact of the crisis as experienced by the individual further increases this risk. The perceived impact of the recession was here a stronger correlate of suicidal risk than actual financial difficulties, such as income reduction. The perceived experience of an economic recession is obviously subjective and has a variable impact on individuals (115). The perceived impact of the financial crisis may provide an indication of how individuals cope with the crisis, since individuals may experience financial crises in different ways depending on a combination of interacting factors such as gender, income, numeracy and political attitude (116). Our findings indicate that the perceived impact of the crisis may increase suicidal risk in patients with LTCs diagnosed with major depressive disorder, and even though it may be challenging for healthcare professionals to intervene in financial crises, negative health effects may be addressed by specifically targeting the perceived impact of the recession in vulnerable patients.

The results of the baseline study showed that in patients with LTCs but not in those without LTCs S-carriers presented with more depressive symptoms. This finding indicates that a vulnerable substrate is important not for the development of depression *per se*, but acts in combination with a stressor, i.e., a medical illness, to increase the risk for depression development. Other correlates of depressive symptoms in the patient group should also be taken into account as risk factors, such as younger age, lower education, lower psychological resources, i.e. resilience and, especially, sense of coherence, and dysfunctional coping strategies, i.e. negative religious coping. Importantly, several illness perceptions were also associated with depressive symptoms, and this may have important clinical implications, as illness perceptions are modifiable and psychotherapeutic strategies to improve illness representations may have the potential to prevent depression development.

We found that all outcomes (i.e. depressive symptom severity, suicidal risk, health-related quality of life) significantly improved six months after the initiation of the study and the application of our low-intensity intervention. We cannot be sure whether this improvement is based exclusively on our intervention, as the design of our study prevents us for fair conclusions to be drawn on this issue. However, these findings provide evidence regarding the identification of the major therapeutic factors for reducing depressive symptoms in patients with LTCs.

Present findings showed that, in patients with LTCs, greater sense of coherence, lower perceptions regarding the consequences of the medical illness and better perception of the identity of the illness were the variables most closely associated with improvement in depressive symptom severity between baseline and follow-up. In addition, although its relationship with improvement of depressive symptoms was rather weak, a vulnerable substrate in the 5-HTTLPR genotype should not be underestimated as far as its contribution to depression development under stress (i.e. a medical illness).

Finally, most findings of the qualitative study regarding the prediction of depression development confirm our quantitative findings. In addition, the findings of the qualitative study highlighted other contributions not measured in the quantitative study, such as pain and fatigue. In addition, it revealed that many individuals living with chronic disease never discuss their condition with their physicians and, although our participants discussed a variety of coping methods for depression, they did not generally discuss their depression with others. Individuals living with chronic disease need to be encouraged to discuss their symptoms with their physicians, so that they are more likely to receive appropriate clinical attention and treatment. Barriers to detecting and managing depression in patients with LTCs are related to patients' and practitioners' failure to recognize depression, a propensity to normalize distress in the face of LTCs. Improvements in the quality of care for depression in patients with LTCs are likely to follow on from interventions that support and facilitate practitioners to engage patients in more collaborative management strategies.

5. *Understanding who is resilient to or at risk for MDD and what are the major therapeutic factors for enhancing resilience and reducing depressive symptoms*

In summary, the results of the present study identified the following risk and protective factors for depression in people with chronic medical illnesses in the era of the current Greek recession:

A. <u>Risk factors (in descending order)</u>
    a. Increased worries about the consequences of the medical illness
    b. Greater adoption of negative religious coping
    c. A combination of greater perceived impact and major depression significantly increases the suicide risk

d. A combination of a medical diagnosis with substrate vulnerability in the 5-HTTLPR genotype increases the risk for depression; this risk is further increased when two medical illnesses are present
e. Greater perceived impact of the recession
f. Younger age
g. Lower education received
h. Greater illness concern
i. Pain and fatigue (not evidenced in the raw, as they are based on the findings of the qualitative study)

B. Protective (enhancing resilience to depression) factors ((in descending order)
   a. Higher levels of Sense of Coherence
   b. Better perception of the identity of the illness
   c. Higher levels of resilience as defined in the Resilience scale
   d. Greater use of positive religious coping
   e. Older age
   f. Higher education received
   g. Higher beliefs regarding their personal and treatment control over the illness
   h. Better comprehension of the illness (combined with the results of the qualitative study found that depressed patients face difficulties in discussing their condition with the physician)

The feasibility of introducing the clinical prediction rule care intervention into the medical setting is supported in four ways. First, the response rate at baseline was high, reaching up to 86.3% in patients with LTCs. Second, the dropouts in the six-month follow-up after the initiation of the study and intervention were low (25.1%), while the majority of dropouts were residents in distant places in Greece and they were visiting the hospital sporadically, making their re-approach very difficult. Third, all outcomes were improved between baseline and follow-up in the patient sample, indicating that, at least partly, our interventions were feasible and beneficial. Finally, the collaboration of the researchers with clinicians was excellent, and this is further supported by the fact that several clinicians not initially participated in the study asked later to participate; the good collaboration with the clinicians and the good

researcher-participant relationships are also reflected in the high response rate, especially as far as the participation to follow-up is concerned.

Present findings suggest that specific therapeutic attention should be given to younger and lower educated patients with chronic illnesses, especially those who face additional difficulties due to the current recession (i.e. greater income reduction, greater perceived impact of the crisis), as they were found at some greater risk for depression. Studies in the primary care setting provided evidence that younger patients may be more vulnerable to psychological distress, in line with the present findings (117-119). Our findings are further supported by a study from eight US primary care sites (120). This investigation has found that while older patients had two to three times more chronic medical conditions, the older group had significantly lower psychological distress symptoms (120). It is possible that older people may experience illness as a consequence of aging and therefore expect to face chronic diseases as they grow older. On the other hand, chronic illness is not usually anticipated in younger age, and younger patients may experience more distress when coping with illness because they have increased responsibilities (e.g., work, rising children), which can be restricted by the presence of a severe chronic illness.

Religiousness may also play a role here; it has been suggested that as people age, aspects of spirituality or religion sometimes increase or become more important in these patients' lives and that older people tend to be more religious (121). Also, in Greek-Orthodox religion a disease is often perceived as 'God's will', thereby promoting a stoic– prone attitude; it has been also pointed out that religiousness has an important beneficial effect on depressive symptoms (122), and present findings further support this assumption, since we found here that greater adoption of negative religious coping predicts depression worsening in a six-month period, while adoption of positive religious coping is associated with lower depressive symptom severity.

Our findings also underscore the need to assess and manage depressive disorders in patients with LTCs within the medical setting. Clinicians should pay special attention in the presence of depressive symptoms symptoms in patients with LTCs, in order to prevent an additional emergence of suicidality triggered by the current Greek social and financial crisis, as present findings showed. Ensuring appropriate systems, services and support for chronic patients with mental disorders should be a priority for health professionals in the era of the current recession.

Finally, present findings indicate that a psychotherapeutic approach to prevent or to treat depressive symptoms in patients with LTCs in the era of the current Greek crisis should be four-fold:

a) Clinicians and other health care providers should bear in mind that symptoms of depression need to be adequately addressed across the entire life span, paying greater attention to younger patient groups with chronic physical illnesses in order to prevent further functional deterioration. However, whether screening for depression in the medical setting would lead to increased treatment of depression remains to be established, since screening might be pointless unless those patients with more severe depressive symptoms are adequately treated. The US Preventive Services Task Force has recommended that although screening in itself is not effective in influencing treatment outcome, there is evidence for the efficacy of integrated care for depression when screening is coupled with system changes that help ensure adequate treatment and follow up for depression (123-124). Therefore, in addition to the suggested further education and training for physicians and the use of effective strategies to cope with practice barriers and constraints in addressing and responding to the patients' psychological needs (125), the establishment of a constant liaison between the medical health care team and the consultation-liaison psychiatry team in developing and implementing interventions for the depressed patients could prove highly beneficial in the management of the depressive symptomatology. This implementation of effective screening and management of depression may render the practice of medicine essential in improving and sustaining the patient's well-being.

b) Clinicians should also consider the chronic patients' patients' illness representations and refer them for psychotherapeutic interventions. B-IPQ may be a useful and time-efficient tool for physicians to assess illness representations. The design of psycho-educational therapies targeting illness representations in patients with LTCs is an important perspective opened by the present study and may have a beneficial effect upon the patients' mental health. Cognitive behavioural therapy (CBT) targeting illness cognitions might be effective for medical patients. Evidence suggests that, in patients with arthritis, CBT can change illness representations resulting in better outcomes (126). In addition,

patients' education may increase their understanding about the disease and therefore can improve outcome, a finding previously described in RA (127).

c) Present findings indicate that, a strong sense of coherence (SOC) enhances patients' well-being in the short term, further confirming previous suggestions that medical interventions should not only be aimed at alleviating the disease but also at improving health by strengthening a person's SOC and by placing at the center of the therapeutic process the principles of person-centered medicine (128). Although it is believed that SOC develops usually in the first 3 decades of life, it is not a static orientation (128) and it can be strengthened through personal activity and care (129), psychodynamic psychotherapy (130) or group-based cognitive behavioral therapy, which has been shown that, in people with chronic medical conditions, enhances SOC and promotes well-being (131). Therefore, it is essential for physicians to be able to identify patients with difficulties in coping with chronic illness; SOC scale could be a useful and time-efficient method to detect psychologically vulnerable patients and refer them for psycho- educational and/or psychotherapeutic interventions to prevent the development of psychopathology and deterioration of quality of life.

d) Attention should also be given to the patient's coping abilities as well as their psychological resources to deal with the stressor could shape those responses. *Resilience* may constitute a key element in this respect, with regard to the way a person will respond during and after the occurrence of an adverse life event (132-136), such as a chronic illness or a financial crisis. Studies have shown that appropriate training in resilience-building strategies can help students build greater awareness of resilience, and potentially support their development of a more resilient approach in their personal and professional lives (137).

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Table 1. Participants' characteristics and crisis parameters across the two samples.

	Patients with LTCs (N=229)	**Participants without LTCs (N=110)**	**Sign.**
Age (mean ± SD)	58.9 ± 13.8	38.7 ± 9.5	p<0.001 [(a)]
Sex (N, %)			p<0.001 [(b)]
Females	101 (44.1%)	85 (77.3%)	
Males	128 (55.9%)	25 (22.7%)	
Divorced/widowed/separated	27 (11.8%)	6 (15.5%)	p=0.065 [(b)]
Education			p<0.001 [(b)]
Below basic education	13 (5.5%)	0	
Elementary (9 years)	115 (50.2%)	3 (2.7%)	
High-School (12 years)	64 (27.9%)	32 (29.1%)	
College/University	37 (16.2%)	75 (68.2%)	
Occupation			p<0.001 [(b)]
Worker	3 (1.3%)	-	
Farmer	6 (2.6%)	-	
Self-employed	14 (6.1%)	1 (0.9%)	
Private employee	16 (7.0%)	4 (3.6%)	
Civil servant	15 (6.6%)	83 (75.5%)	
Pensioner	127 (55.5%)	-	
Householder	20 (8.7%)	-	
Other	9 (3.9%)	22 (20%)	
Unemployed (N, %)	19 (8.3%)	0	p=0.007 [(b)]
Unemployment due to ill health (pensioned; N, %)	51 (26.8%)	0	p<0.001 [(b)]
Job lost due to the financial crisis (N, %)	12 (6.2%)	0	p=0.010 [(b)]
Percentage of income reduction during the last 2 years (mean±SD)	33.8 ± 22.0	29.3 ± 15.3	p<0.001 [(a)]
Perceived impact of crisis (mean±SD)	6.3 ± 2.1	6.0 ± 2.3	p=0.226 [(a)]
Resilience (RS-14)	79.23 12.1	81.3 12.0	p=0.140 [(a)]
Sense of coherence (SOC)	136.44 25.0	143.4 23.6	P=0.019 [(a)]
History of mental illness (N, %)	65 (28.5%)	18 (18.8%)	p=0.066 [(b)]

(a) Two-tailed t-test; (b) chi-square test

Table 2. Prevalence of Mental Disorders at baseline according to the MINI interview

	Participants without LTCs (N=110)	**Patients with LTCs (N=229)**	**p [(a)]**
Major depressive disorder	12 (10.9%)	54 (23.6%)	<0.001
Dysthymia	4 (3.6%)	17 (7.4%)	0.176
Suicide risk	2 (1.8%)	33 (14.4%)	<0.001
Low	2 (1.8%)	25 (10.9%)	0.002
Moderate	0	8 (3.5%)	
High	0	0	
Panic disorder	1 (0.9%)	15 (6.5%)	0.022
Generalized anxiety disorder	3 (2.7%)	45 (19.6%)	<0.001
Agoraphobia	0	11 (4.8%)	0.019
Any mental disorder	23 (20.9%)	113 (49.3%)	<0.001

(a) chi-square test

Table 3. Prevalence of Mental Disorders across gender at baseline according to the MINI interview

	Patients with LTCs (N=229)			Participants without LTCs (N=110)		
	Male (N=128)	**Female (N=101)**	**p [(a)]**	**Male (N=25)**	**Female (N=85)**	**p [(a)]**
Major depressive disorder	24 (18.7%)	30 (29.7%)	0.116	3 (12.0%)	9 (10.6%)	0.983
Dysthymia	12 (9.4%)	5 (4.9%)	0.205	0	4 (4.7%)	0.269
Suicide risk	12 (9.4%)	21 (20.8%)	0.015	1 (4.0%)	1 (1.2%)	0.353
Low	8 (6.2%)	17 (16.8%)	0.034	1 (4.0%)	1 (1.2%)	0.353
Moderate	4 (3.1%)	4 (3.9%)		0	0	
High	-	-		0	0	
Panic disorder	6 (4.7%)	9 (8.9%)	0.200	0	1 (1.2%)	0.586
Generalized anxiety disorder	22 (17.2%)	23 (22.8%)	0.310	0	3 (3.5%)	0.316
Agoraphobia	6 (4.7%)	5 (4.9%)	0.937			
Any mental disorder	61 (47.7%)	52 (51.5%)	0.565	3 (12.0%)	20 (23.5%)	0.213

(a) chi-square test

Table 4. Frequencies of 5-HTTLPR genotypes across health and disease

	Participants without LTCs (N=110)	**Patients with LTCs (N=229)**	**p [(a)]**
LL Homozygous	41 (37.3%)	79 (34.5%)	0.761
LS	53 (48.2%)	110 (48.0%)	
SS	16 (14.5%)	40 (17.5%)	
S-carriers	69 (62.7%)	150 (65.5%)	0.617

(a) chi-square test

Table 5. Frequencies of 5-HTTLPR genotypes across MINI diagnosis of MDD

	Participants without MDD (N=273)	**Participants with MDD (N=66)**	**p [(a)]**
LL Homozygous	94 (34.4%)	26 (39.4%)	0.669
LS	132 (48.4%)	31 (47.0%)	
SS	47 (17.2%)	9 (13.6%)	
S-carriers	179 (65.6%)	40 (60.6%)	0.449

(a) chi-square test

Table 6. Factors associated with depressive symptom severity in health and disease at baseline

	Participants without LTCs (N=110)		**Patients with LTCs (N=229)**	
	beta	**p**	**beta**	**p**
Demographics				
Age	.140	.153	-.097	.318
Sex	-.047	.583	-.045	.415
Education	-.154	**.063**	-.062	.338
Divorced/widowed/separated	-050	.608	.027	.615
Genetic background				
S-carriers	.100	.229	.101	**.049**
Crisis parameters				
Unemployment	.047	.578	.034	.529
Income reduction	.087	.328	.018	.756
Perceived impact of crisis	.047	.602	.036	.529
Psychological parameters				
Resilience	-.004	.602	-.105	.079
Sense of coherence	-.517	**.001**	-.418	**.001**
Positive religious coping	-.170	**.079**	-.040	.489
Negative religious coping	.142	.140	.119	**.037**
Illness perceptions (patients only)				
Consequences	-	-	.039	.575
Timeline	-	-	.020	.695
Personal control	-	-	-.023	.676
Treatment control	-	-	-.031	.584
Identity	-	-	.265	**.001**
Concern	-	-	.011	.863
Comprehension	-	-	-.077	.157
Comorbidities (Charlson index)	-	-	.039	.676
R square adjusted	.327		.448	

Note: Linear multiple regression analyses with dependent variable the PHQ-9 score improvement between baseline and follow-up adjusted for age, sex, education, and marital status

Table 7a. Changes in outcomes between baseline and t1 in the total sample

	Baseline	**T1**	**p**
PHQ-9	5.82 ± 5.18	4.15 ± 4.64	<0.001
RASS	154.32 144.25	145.38 138.74	0.215
Physical HRQoL	63.06 ± 19.1	63.6 ± 20.5	0.487
Mental HRQoL	66.62 ± 16.22	67.75 ± 16.2	0.152
Social Relations HRQoL	62.81 ± 21.7	59.95 ± 22.4	0.007
Environment HRQoL	63.86 ± 12.0	66.73 ± 10.8	<0.001

Note: mean ± SD; paired t-test)

Table 7b. Changes in outcomes between baseline and t1 in the patient sample

	Baseline	**T1**	**p**
PHQ-9	6.64 ± 5.32	4.72 ± 5.01	<0.001
RASS	165.87 145.47	178.78 147.53	0.156
Physical HRQoL	55.38 ± 16.71	54.54 ± 18.06	0.412
Mental HRQoL	64.62 ± 17.0	63.58 ± 16.78	0.316
Social Relations HRQoL	58.63 ± 20.87	52.43 ± 20.51	<0.001
Environment HRQoL	64.39 ± 11.96	66.28 ± 9.98	0.019

Note: mean ± SD; paired t-test)

Table 7c. Changes in outcomes between baseline and t1 in the healthy participant sample

	Baseline	**T1**	**p**
PHQ-9	4.13 ± 4.42	3.0 ± 3.53	<0.001
RASS	131.45 139.66	79.18 88.08	<0.001
Physical HRQoL	78.37 ± 13.57	81.62 ± 11.12	0.002
Mental HRQoL	70.61 ± 13.78	76.06 ± 10.93	<0.001
Social Relations HRQoL	71.13 ± 21.10	74.92 ± 18.21	0.012
Environment HRQoL	62.81 ± 12.18	67.64 ± 12.33	<0.001

Note: mean ± SD; paired t-test)

Table 8. Predictors of change (improvement) in depressive symptom severity between baseline and follow-up in health and disease

	Participants without LTCs (N=110)		**Patients with LTCs (N=229)**	
	beta	**p**	**beta**	**p**
Genetic background				
S-carriers	-.181	**.058**	-.127	**.059**
Crisis parameters				
Unemployment	-	-	-.056	.425
Income reduction	-.070	.489	-.030	.700
Perceived impact of crisis	-.032	.755	-.099	.183
Psychological parameters				
Resilience	.052	.643	.037	.633
Sense of coherence	.342	**.003**	.206	**.013**
Positive religious coping	.132	.227	.137	**.073**
Negative religious coping	-.120	.271	-.017	.820
Illness perceptions (patients only)				
Consequences	-	-	-.241	**.009**
Timeline	-	-	-.059	.379
Personal control	-	-	.112	.124
Treatment control	-	-	.061	.410
Identity	-	-	.185	**.037**
Concern	-	-	-.055	.509
Comprehension	-	-	.003	.963
Comorbidities (Charlson index)	-	-	-.023	,849
R square adjusted	.223		.146	

Note: Linear multiple regression analyses with dependent variable the PHQ-9 score improvement between baseline and follow-up adjusted for age, sex, education, and marital status