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Vitality, mental health and role-physical mediate the influence of coping on depressive symptoms and self-efficacy in patients with non-alcoholic fatty liver disease: A cross-sectional study

Jesús Funuyet-Salas [a,*], María Ángeles Pérez-San-Gregorio [a], Agustín Martín-Rodríguez [a], Manuel Romero-Gómez [b]

[a] Department of Personality, Assessment, and Psychological Treatment, Faculty of Psychology, University of Seville, Seville, Spain
[b] UCM Digestive Diseases and Ciberehd, Virgen del Rocío University Hospital, Institute of Biomedicine of Seville, University of Seville, 41013 Seville, Spain

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ABSTRACT

Objective: Our aim was to determine whether the association between active coping and depressive symptoms in patients with non-alcoholic fatty liver disease (NAFLD) was mediated by vitality, and whether diabetes and obesity could impact on this relationship. We also wanted to find out whether mental health and role-physical modulated the relationship between passive/avoidance coping and self-efficacy, and the role of liver fibrosis.
Methods: Depressive symptoms (BDI-II), self-efficacy (GSE), coping (COPE-28) and quality of life (SF-12) were evaluated in 509 biopsy-proven NAFLD patients in this cross-sectional study. Mediation and moderated mediation models were conducted using the SPSS PROCESS v3.5 macro.
Results: Vitality mediated the relationship between active coping and depressive symptoms (−2.254, CI = −2.792 to −1.765), with diabetes (−0.043, $p = 0.017$) and body mass index (BMI) (−0.005, $p = 0.009$) moderating the association. In addition, mental health (−6.435, CI = −8.399 to −4.542) and role-physical (−1.137, CI = −2.141 to −0.315) mediated the relationship between passive/avoidance coping and self-efficacy, with fibrosis stage (0.367, $p < 0.001$) moderating this association. Specifically, the presence of diabetes and significant fibrosis, and a higher BMI, were associated with greater negative impact on participant depressive symptoms or self-efficacy.
Conclusion: A maladaptive coping style was associated with poorer vitality, mental health and role-physical in NAFLD patients, which along with the presence of metabolic comorbidity (diabetes and obesity) and significant fibrosis predicted more depressive symptoms or poorer self-efficacy in these patients. These results suggested incorporating emotional and cognitive evaluation and treatment in patients with NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) represents a wide clinical spectrum of chronic liver pathologies, from liver steatosis to non-alcaholic steatohepatitis (NASH), liver cirrhosis and hepatocellular carcinoma, finally requiring liver transplantation [1]. It is estimated that from 10 to 15% of NAFLD patients have liver fibrosis, which is an important predictor of the patient's clinical and psychosocial profile [2–4].

In recent years, there has been growing interest in study of patient-reported outcomes (PROs) in NAFLD, to find out the patient's perspective of his health condition and wellbeing [5]. NAFLD is associated with a worse quality of life, mainly related to physical functioning, with patients who often refer to problems such as fatigue or lack of vitality [6,7]. NAFLD patients have also been found to have more depressive symptoms than other chronic liver pathologies [8]. A multiple linear regression analysis of 307 patients with biopsy-proven NAFLD was performed to determine the influence of coping strategies on their perceived health. Results showed that strategies commonly associated with an active coping style, such as active coping, positive reframing and acceptance, predicted better quality of life of NAFLD patients. On the contrary, strategies commonly associated with a

* Corresponding author at: Faculty of Psychology, Department of Personality, Assessment, and Psychological Treatment, C/ Camilo José Cela s/n, 41018 Seville, Spain.
E-mail addresses: jfunuyet1@us.es (J. Funuyet-Salas), anperez@us.es (M.Á. Pérez-San-Gregorio), amartinr@us.es (A. Martín-Rodríguez), mromerogomez@us.es (M. Romero-Gómez).

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passive/avoidance coping style such as self-distraction, disengagement, denial and self-blame predicted unsatisfactory perception of their state of health and wellbeing [9].

NAFLD is closely associated with metabolic syndrome components, especially type 2 diabetes mellitus (T2DM) and obesity, such that when both pathologies coexist, they usually interact with each other worsening the patient's prognosis and clinical evolution [10,11]. In fact, the presence of T2DM or obesity has been related to a worse quality of life and/or more maladaptive coping by those diagnosed with NAFLD [9,12]. However, the influence metabolic comorbidity could have on the mental health of these patients is unknown.

Furthermore, intervention in NAFLD focuses on weight loss through changes in life style, including diet, exercise and physical activity [13]. Therapeutic guidelines include resistance training or 150 to 200 min of moderate-intensity aerobic physical activity in three to five weekly sessions. In addition, a Mediterranean diet limiting foods with a high saturated fat or sugar content is also recommended [13,14]. However, therapeutic adherence rates by these patients are quite low with less than half generally adhering to the therapeutic guidelines. [15]. In this respect, depressive symptoms and self-efficacy have recently been identified as determining factors for therapeutic adherence in NAFLD. On one hand, greater presence of depressive symptoms mediates the negative effects of low social support and poor physical quality of life on following instructions on diet and physical activity, respectively [16]. On the other, high perceived self-efficacy has been found to exert a protective role in therapeutic adherence by NAFLD patients with an at-risk psychosocial profile [16], and is a fundamental condition for maintaining long-term weight loss through diet and physical activity [17].

As there is hardly any information available on variables predicting depressive symptoms or self-efficacy of NAFLD patients, understanding the mechanisms that determine their mental health and self-efficacy would contribute to the design and development of NAFLD-specific intervention programmes, providing added value for improving therapeutic adherence rates in this population. Moving from standardised and generic clinical interventions, in which patients are only encouraged to follow therapeutic guidelines, to specific programmes where particularities, strengths and weaknesses of the target population are addressed, would boost the effectiveness of the intervention. It is therefore essential to determine whether clinical characteristics, such as liver fibrosis, or metabolic characteristics, such as T2DM or obesity, are risk factors for the mental health or self-efficacy of NAFLD patients. This would also facilitate screening in healthcare settings by identifying vulnerable patient groups for intervention.

In addition, in-depth understanding of the impact of any disease on the patient's physical, mental and social well-being and functioning can help health and governmental institutions in estimating and allocating economic and care resources [18]. This is particularly important for NAFLD, which is associated with significant economic costs and considerable use of healthcare resources worldwide, and is expected to increase in the coming years due to the growing incidence of metabolic syndrome and NASH in children [19].

In this context, we proposed exploring how depressive symptoms, self-efficacy, active coping, passive/avoidance coping, vitality, mental health, role-physical and body mass index (BMI) are interrelated in NAFLD patients. We also wanted to know on one hand, whether there were statistically significant differences in depressive symptoms, active coping and vitality based on presence or absence of T2DM, and on the other, if there were statistically significant differences in self-efficacy, passive/avoidance coping, mental health and role-physical based on presence or absence of significant fibrosis. We further examined whether vitality mediates the relationship between active coping and depressive symptomatology, and whether T2DM and BMI moderate that relationship. And finally, we analyzed whether the mental health and role-physical mediate the relationship between passive/avoidance coping and self-efficacy, and whether significant fibrosis has a moderating effect on this relationship.

2. Methods

2.1. Participants

Our sample consisted of 509 patients with biopsy-proven NAFLD (300 men and 209 women) with a mean age of 55 ± 12 years. This cross-sectional study was approved by the Ethics Committee of the Virgen del Rocío University Hospital of Seville. All the patients, whose sociodemographic characteristics are provided in Table 1, gave their written informed consent to participate. This study met the Helsinki Declaration 1964 guidelines of good practice.

Table 1
Univariate analises of the differences in depressive symptoms and self-efficacy by sociodemographic and clinical variables.

	M (SD)	Depressive symptoms *M (SD)*	*r* (*p*)	Self-efficacy *M (SD)*	*r* (*p*)
Age	55.1 (11.8)	7.02 (7.89)	0.157 (<0.001)	65.07 (18.31)	−0.163 (<0.001)
	Total N (%)	Depressive symptoms *M (SD)*	*t* / *U* (*p*)	Self-efficacy *M (SD)*	*t* / *F* (*p*)
Gender			$t_{(1,350.952)} = -4.978$		$t_{(1,396.966)} = 4.843$
- Male	300 (58.9)	5.52 (6.51)	(<0.001)	68.37 (16.55)	(<0.001)
- Female	209 (41.1)	9.18 (9.13)		60.33 (19.65)	
Marital status			$t_{(1,507)} = 0.476$		$t_{(1,151.305)} = -1.191$
- With partner	401 (78.8)	6.94 (7.70)	(0.634)	65.62 (17.60)	(0.236)
- Without partner	108 (21.2)	7.34 (8.59)		63.03 (20.68)	
Education			$U_{(2,314.092)} = 10.017$		$F_{(2,506)} = 18.218$
- Low	226 (44.4)	8.46 (8.26)	(<0.001)	60.18 (18.25)	(<0.001)
- Medium	148 (29.1)	6.76 (7.94)		66.63 (17.77)	
- High	135 (26.5)	4.90 (6.66)		71.55 (16.72)	
Employment			$t_{(1,486.042)} = -6.654$		$t_{(1,495.918)} = 7.335$
- Working	242 (47.5)	4.71 (6.29)	(<0.001)	70.95 (15.06)	(<0.001)
- Not working	267 (52.5)	9.12 (8.59)		59.73 (19.35)	
NASH			$t_{(1,507)} = -1.739$		$t_{(1,507)} = 0.875$
- Absence	276 (54.2)	6.46 (7.45)	(0.083)	65.72 (17.49)	(0.382)
- Presence	233 (45.8)	7.68 (8.35)		64.30 (19.23)	
Significant fibrosis			$t_{(1,303.458)} = -5.553$		$t_{(1,331.142)} = 5.396$
- Absence	317 (62.3)	5.43 (6.44)	(<0.001)	68.58 (15.95)	(<0.001)
- Presence	192 (37.7)	9.65 (9.27)		59.28 (20.40)	

The Pearson's correlation (age), *t*-test for independent samples (gender, marital status, employment, NASH, significant fibrosis), and analysis of variance (education) were applied.

2.2. Measurements

The *Beck Depression Inventory-II* (BDI-II) measures severity of depressive symptoms in the past two weeks [20]. The instrument, comprised of 21 items rated on a four-point Likert-type scale (except Items 16 and 18, which have seven points), provides a total score corresponding to the sum of scores on each of the items, which may vary from 0 to 63. The higher the score, the more severe the depressive symptoms are. We used the Spanish version of the instrument [21], which had a Cronbach's alpha of 0.91.

The *General Self-Efficacy Scale* (GSE) measures how a person perceives their own ability to manage and face stressful everyday situations [22]. The instrument, comprised of 10 items answered on a ten-point Likert-type scale provides a total score from the sum of scores on each item, which can vary from 10 to 100. The higher the score, the greater self-efficacy is. We used the Spanish version of the instrument [23], which had a Cronbach's alpha of 0.94.

The *Brief COPE* (COPE-28) evaluates coping strategies usually used by a person to face problems or difficult situations [24]. In this study, seven of these strategies were selected to establish two dimensions according to participant coping style. Based on the results of a previous study [9], active coping, positive reframing and acceptance made up an active, or adaptive, coping style, while self-distraction, disengagement, denial and self-blame constituted a passive/avoidance or maladaptive coping style. The instrument, made up of 28 items with four-point Likert-type scales, provide a score for each one of the coping strategies, which can vary from 0 to 3. The higher the score, the more the coping strategy is used. We used the Spanish version of the instrument [25], which had a Cronbach's alpha of 0.82–0.96 for the different subscales used.

The *12-Item Short Form Health Survey* (SF-12v.2) measures health-related quality of life [26,27]. The instrument is composed of 12 items with three or five-point Likert-type scales, providing a score for each of the following dimensions of health-related quality of life: physical functioning, general health, social functioning, bodily pain, role-physical, role-emotional, vitality, and mental health. The vitality dimension determines the patient's fatigue and energy levels: "How much of the time during the past four weeks did you have a lot of energy?" This dimension was analyzed as a measure of participant fatigue, which is the main symptom associated with NAFLD [28]. The role-physical dimension determines how much physical health interferes with the patient's functioning: "During the past four weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?" This dimension was analyzed as a measure of participant physical health. The mental health dimension determines how the patient has been feeling emotionally during the past weeks: "These questions are about how you feel and how things have been with you during the past four weeks. For each question, please give the one answer that comes closest to the way you have been feeling." This dimension was analyzed as a measure of participant mental health. Their scores vary from 0 to 100, from a worse to a better state of health, respectively. The higher the score, the better the health-related quality of life. In our sample, the Cronbach's Alpha for the various dimensions employed was 0.72–0.94.

2.3. Procedure

Starting from an original sample of 755 NAFLD patients from 12 Spanish hospitals, 509 were finally selected (102 were excluded because they did not want to participate in the study and 81 because they had undergone bariatric surgery either before or after the liver pathology diagnosis, 35 due to incomplete data on the biopsy report, and 28 for multimorbidity). Sample inclusion requirements were to be of legal age, have given their informed consent to participate in the study, understand the study evaluation instruments, have been diagnosed with NAFLD by liver biopsy, not have undergone bariatric surgery either before or after the liver pathology diagnosis, and not have any severe or disabling psychopathology. The whole evaluation was carried out by the same psychologist who employed the same evaluation instruments in the same order for all participants: psychosocial interview, SF-12, BDI-II, COPE-28 and GSE. Fibrosis and NASH were diagnosed by liver biopsy. T2DM was diagnosed by glycated haemoglobin (HbA1c). Obesity was diagnosed by the BMI resulting from measuring the patient's height and weight.

2.4. Statistical analysis

The independent samples *t*-test and analysis of variance (ANOVA) were applied to examine the differences in depressive symptoms and self-efficacy of the participants by their sociodemogaphic (gender, age, marital status, education, employment) and clinical (NASH and liver fibrosis) characteristics. Education was coded as low (up to age 16), medium (up to 16–18) or high (higher education).

Pearson's correlations were employed to analyze the associations between depressive symptoms, self-efficacy, active coping, passive/avoidance coping, vitality, mental health, role-physical and BMI. To analyze the differences in these variables by absence or presence of T2DM and significant fibrosis, the independent sample *t*-test was applied. Cohen's *d* was calculated as the effect size index.

Mediation and moderated mediation models were estimated using the SPSS PROCESS macro v3.5 [29]. First, vitality was analyzed as a mediator in the relationship between active coping and depressive symtoms, using Model 4 [30]. Then Model 6 was applied to test whether the mental health and role-physical mediated the relationship between passive/avoidance coping and self-efficacy. In both cases bootstrapping with 5000 resamples was employed to test the indirect effects estimated. The mediation effect was considered significant when the confidence interval (CI) of 95% of the indirect effects did not include 0. In continuation, Model 16 [30] was used, again with bootstrapping with 5000 resamples, to analyze the moderated mediation effect, that is, whether T2DM and the BMI moderated the indirect effects of active coping, through vitality, on depressive symptoms. Model 91 was applied to test whether significant fibrosis moderated the indirect effects of passive/avoidance coping, through mental health and role-physical, on self-efficacy.

Pick-a-point with the PROCESS macro was used to test the significance of the moderation effect. This technique provides three quantitative moderator groups, classifying participants as low, medium or high in that variable. Finally, for each of those values, the conditional effect of the predictor variable on the criterion variable was calculated, generating a confidence interval for it [31]. A two-sided p-value <0.05 was considered statistically significant.

3. Results

3.1. Sociodemographic and clinical variables

The 509 participants had a mean age of 55.1 ($SD = 11.8$), 58.9% were men and 41.1% women. Of these, 78.8% had a partner, 44.4% low education, 47.5% were actively employed, 45.8% had NASH and 37.7% had significant fibrosis (F2-F4). The mean score for depressive symptoms was 7.02 ($SD = 7.89$), while for self-efficacy it was 65.07 ($SD = 18.31$). The results of the independent samples *t*-test and ANOVA showed that the scores on depressive symptoms and self-efficacy were significantly different ($p < 0.001$) by gender, education, employment and fibrosis. There was also a significant correlation ($p < 0.001$) between age and scores in depressive symptomatology and self-efficacy (Table 1).

3.2. Correlation analysis

The most important results revealed by the Pearson correlation

Table 2
Differences in depressive symptoms, active coping and vitality as a function of type 2 diabetes mellitus (absence or presence).

	General	T2DM		Intergroup comparisons	Effect sizes
	$n = 509$	Absence $n = 345$	Presence $n = 164$		
Variables	*M (SD)*	*M (SD)*	*M (SD)*	*t* (*p*)	Cohen's *d*
1. Depressive symptoms	7.02 (7.89)	5.84 (6.82)	9.51 (9.31)	$t_{(1,249.219)} = -4.512$ (<0.001)	−0.45 S
2. Active coping	1.71 (0.75)	1.77 (0.71)	1.59 (0.83)	$t_{(1,279.944)} = 2.468$ (0.014)	0.23 S
3. Vitality	56.39 (27.86)	59.86 (25.37)	49.09 (31.32)	$t_{(1,268.235)} = 3.845$ (<0.001)	0.38 S

S small effect size.
The independent sample *t*-test was applied.

Table 3
Differences in self-efficacy, passive/avoidance coping, mental health and role-physical as a function of significant fibrosis (absence or presence).

	General	Significant fibrosis		Intergroup comparisons	Effect sizes
	$n = 509$	Absence $n = 317$	Presence $n = 192$		
Variables	*M (SD)*	*M (SD)*	*M (SD)*	*t* (*p*)	Cohen's *d*
1. Self-efficacy	65.07 (18.31)	68.58 (15.95)	59.28 (20.40)	$t_{(1,331.142)} = 5.396$ (<0.001)	0.51 M
2. Passive/avoidance coping	0.46 (0.43)	0.41 (0.40)	0.54 (0.48)	$t_{(1,349.360)} = -3.085$ (0.002)	−0.29 S
3. Mental health	70.09 (22.55)	72.95 (21.76)	65.36 (23.09)	$t_{(1.507)} = 3.724$ (<0.001)	0.34 S
4. Role-physical	76.20 (30.46)	82.89 (25.53)	65.17 (34.54)	$t_{(1,317.294)} = 6.161$ (<0.001)	0.58 M

S small effect size, *M* medium effect size.
The independent sample *t*-test was applied.

analysis were that depressive symptoms were negatively associated with active coping ($r = -0.603$) and vitality ($r = -0.637$) and positively associated with BMI ($r = 0.219$), while self-efficacy was negatively associated with passive/avoidance coping ($r = -0.472$) and positively associated with mental health ($r = 0.551$) and role-physical ($r = 0.481$). Furthermore, active coping was positively associated with vitality ($r = 0.507$) and negatively associated with BMI ($r = -0.193$), while passive/avoidance coping was negatively associated with mental health ($r = -0.521$) and role-physical ($r = -0.352$). Vitality was negatively associated with BMI ($r = -0.218$), while mental health was positively associated with role-physical ($r = 0.486$). All of these correlations were statistically significant ($p < 0.001$).

In addition, the independent samples *t*-test revealed statistically significant differences based on absence or presence of T2DM (Table 2). Thus, diabetic participants had worse depressive symptoms ($p < 0.001$, $d = -0.45$), and less active coping ($p = 0.014$, $d = 0.23$) and vitality ($p < 0.001$, $d = 0.38$). There were also statistically significant diferences by absence or presence of significant fibrosis (Table 3). So, participants with signficant fibrosis referred to lower self-efficacy ($p < 0.001$, $d = 0.51$), mental health ($p < 0.001$, $d = 0.34$) and role-physical ($p < 0.001$, $d = 0.58$), and more passive/avoidance coping ($p = 0.002$, $d = -0.29$).

3.3. Mediation analysis

Fig. 1 shows the significant indirect effect of vitality when it mediates in the association between active coping and depressive symptoms (−2.254, $p < 0.001$). The bootstrap 95% CI did not include 0 (−2.792 to −1.765), confirming the significant indirect effect of active coping on depressive symptoms through vitalitiy. The direct effect of active coping on depressive symptoms was significant after mediation analysis (−3.665, $p < 0.001$), showing partial mediation of vitality.

Fig. 1 also shows the significant indirect effects of mental health and role-physical when mediating in the association between passive/avoidance coping and self-efficacy (mental health, −6.435, $p < 0.001$; role-physical, −1.137, $p = 0.006$; both, −1.435, $p < 0.001$). The bootstrap 95% CI did not include 0 in any of the cases (mental health, −8.399 to −4.542; role-physical, −2.141 to −0.315; both, −2.356 to −0.661),

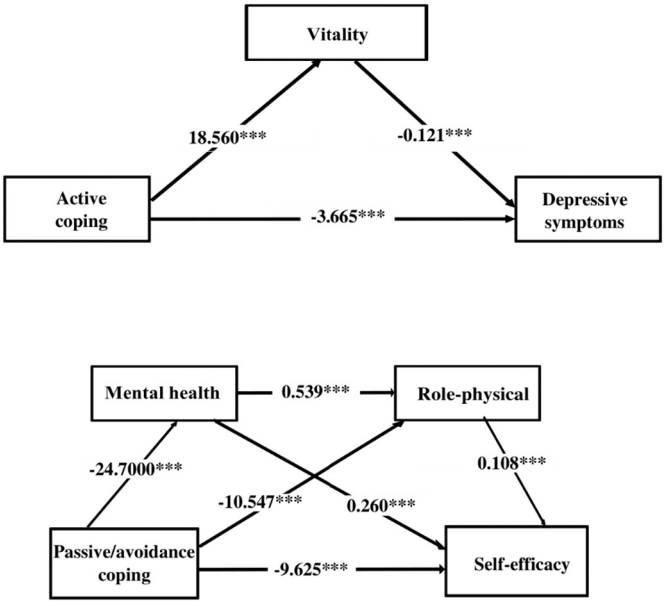

Fig. 1. Vitality mediates the relationship between active coping and depressive symptoms. In addition, mental health and role-physical mediate the relationship between passive/avoidance coping and self-efficacy.
Gender, age, education and employment were entered in the analysis as covariates. The coefficients represent the indirect and direct effects estimated. ***$p < 0.001$.

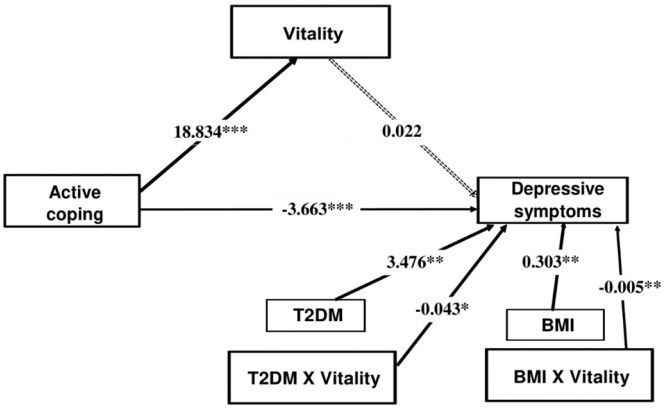

Fig. 2. The moderating effect of T2DM and BMI on the relationship between active coping and depressive symptoms through vitality.
Gender, age, education and employment were entered in the analysis as covariates. The coefficients represent the moderating, indirect and direct effects estimated. *$p < 0.05$; **$p < 0.01$, ***$p < 0.001$.

confirming the significant indirect effect of passive/avoidance coping on self-efficacy through mental health and role-physical. The direct effect of passive/avoidance coping on self-efficacy was significant after mediation analysis (−9.625, $p < 0.001$), showing partial mediation of mental health and role-physical.

3.4. Analysis of moderated mediation

The moderated mediation analyses determined whether T2DM and BMI moderated the effects of active coping on depressive symptoms through vitalitiy on one hand, and on the other, whether significant fibrosis moderated the effects of passive/avoidance coping on self-efficacy through mental health and role-physical.

Fig. 2 shows the results of the moderated mediation model for depressive symptoms. The results revealed that T2DM ($\beta = -0.043$, $p = 0.017$) and BMI ($\beta = -0.005$, $p = 0.009$) moderated the relationship between vitality and depressive symptoms. The pick-a-point technique (Table 4) showed that the negative effects of vitality on depressive symptoms were higher in diabetic patients than in those who were not. They also increased the higher the patient's BMI as measured on three levels: a low BMI, equivalent to a standard deviation below the mean (absence T2DM, effect = −0.073, $p < 0.001$; presence T2DM, effect = −0.116, $p < 0.001$); medium BMI, equivalent to the mean (absence of T2DM, effect = −0.097, $p < 0.001$; presence of T2DM, effect = −0.140, $p < 0.001$); and high BMI, equivalent to one standard deviation above the mean (absence of T2DM, effect = −0.120, $p < 0.001$; presence of T2DM, effect = −0.164, $p < 0.001$).

Table 5 shows the conditional indirect effects of active coping on depressive symptoms through vitality on the levels established for T2DM and BMI. The results showed a larger conditional indirect effect on diabetic participants than on those who were not. There was also a significant increase in the conditional indirect effect as the BMI increased: low BMI (absence T2DM, effect = −1.381, 95% CI = −2.028

Table 4
Moderating effects of type 2 diabetes mellitus (absence or presence) and body mass index on the relationship between vitality and depressive symptoms.

T2DM	BMI	Effect *(SE)*	*t (p)*	Bootstrapped 95% CI	
				Lower	Upper
Absence	25.499 (*M* – 1 *SD*)	−0.073 (0.015)	−4.828 (<0.001)	−0.103	−0.043
Absence	30.636 (*M*)	−0.097 (0.013)	−7.483 (<0.001)	−0.122	−0.071
Absence	35.772 (*M* + 1 *SD*)	−0.120 (0.016)	−7.389 (<0.001)	−0.152	−0.088
Presence	25.499 (*M* – 1 *SD*)	−0.116 (0.017)	−6.699 (<0.001)	−0.151	−0.082
Presence	30.636 (*M*)	−0.140 (0.015)	−9.541 (<0.001)	−0.169	−0.111
Presence	35.772 (*M* + 1 *SD*)	−0.164 (0.017)	−9.612 (<0.001)	−0.197	−0.130

T2DM type 2 diabetes mellitus, *BMI* body mass index, *M* mean, *SD* standard deviation, *SE* standard error, *CI* confidence interval.
The pick-a-point technique was applied to test the significance of the moderating effects.

Table 5
The conditional indirect effect of active coping on depressive symptoms through vitality.

	T2DM	BMI	Effect *(BootSE)*	Bootstrapped 95% CI	
				Lower	Upper
Effect 1	Absence	25.499 (*M* – 1 *SD*)	−1.381 (0.320)	−2.028	−0.771
Effect 2	Absence	30.636 (*M*)	−1.825 (0.323)	−2.512	−1.233
Effect 3	Absence	35.772 (*M* + 1 *SD*)	−2.268 (0.450)	−3.250	−1.470
Effect 4	Presence	25.499 (*M* – 1 *SD*)	−2.194 (0.384)	−2.991	−1.475
Effect 5	Presence	30.636 (*M*)	−2.637 (0.370)	−3.410	−1.952
Effect 6	Presence	35.772 (*M* + 1 *SD*)	−3.081 (0.472)	−4.058	−2.211
Effect 2 – Effect 1			−0.443 (0.219)	−0.884	−0.030
Effect 3 – Effect 1			−0.887 (0.438)	−1.769	−0.060
Effect 4 – Effect 1			−0.813 (0.400)	−1.613	−0.045
Effect 5 – Effect 1			−1.256 (0.442)	−2.149	−0.413
Effect 6 – Effect 1			−1.700 (0.572)	−2.859	−0.608
Effect 3 – Effect 2			−0.443 (0.219)	−0.884	−0.030
Effect 4 – Effect 2			−0.369 (0.469)	−1.286	0.568
Effect 5 – Effect 2			−0.813 (0.400)	−1.613	−0.045
Effect 6 – Effect 2			−1.256 (0.442)	−2.149	−0.413
Effect 4 – Effect 3			0.074 (0.617)	−1.097	1.320
Effect 5 – Effect 3			−0.369 (0.469)	−1.286	0.568
Effect 6 – Effect 3			−0.813 (0.400)	−1.613	−0.045
Effect 5 – Effect 4			−0.443 (0.219)	−0.884	−0.030
Effect 6 – Effect 4			−0.887 (0.438)	−1.769	−0.060
Effect 6 – Effect 5			−0.443 (0.219)	−0.884	−0.030

M mean, *SD* standard deviation, *BootSE* bootstrap standard error, *CI* confidence interval.
Bootstrapping was employed to analyze the conditional indirect effect.

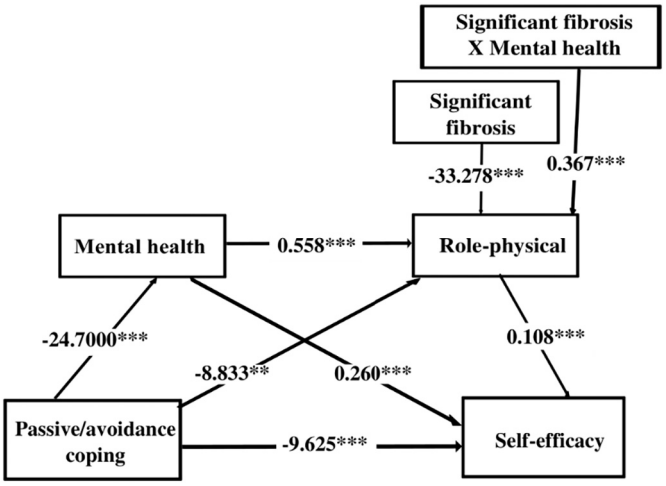

Fig. 3. The moderating effect of significant fibrosis on the relationship between passive/avoidance coping and self-efficacy through mental health and role-physical.
Gender, age, education and employment were entered in the analysis as covariates. The coefficients represent the moderating, indirect and direct effects estimated. $^{**}p < 0.01$, $^{***}p < 0.001$.

Table 6
The moderating effects of significant fibrosis (presence or absence) on the relationship between mental health and role-physical.

Significant fibrosis	Effect *(SE)*	*t (p)*	Bootstrapped 95% CI	
			Lower	Upper
Absence	0.374 (0.070)	5.323 (<0.001)	0.236	0.512
Presence	0.742 (0.084)	8.822 (<0.001)	0.576	0.907

SE standard error, *CI* confidence interval.
The pick-a-point technique was applied to test the significance of the moderating effects.

Table 7
The conditional indirect effect of passive/avoidance coping on self-efficacy through mental health and role-physical.

	Significant fibrosis	Effect *(BootSE)*	Bootstrapped 95% CI	
			Lower	Upper
Effect 1	Absence	−0.996 (0.316)	−1.675	−0.445
Effect 2	Presence	−1.974 (0.611)	−3.257	−0.895
Effect 2 – Effect 1		−0.978 (0.420)	−1.927	−0.281

BootSE bootstrap standard error, *CI* confidence interval.
Bootstrapping was employed to analyze the conditional indirect effect.

to −0.771; presence of T2DM, effect = −2.194, 95% CI = −2.991 to −1.475); medium BMI (absence T2DM, effect = −1.825, 95% CI = −2.512 to −1.233; presence of T2DM, effect = −2.637, 95% CI = −3.410 to −1.952); and high BMI (absence of T2DM, effect = −2.268, 95% CI = −3.250 to −1.470; presence of T2DM, effect = −3.081, 95% CI = −4.058 to −2.211). In the pairwise comparisons between the conditional indirect effects, a strong majority did not include 0 in the bootstrapped 95% CI, confirming that the mediation effect was moderated by T2DM and BMI.

Fig. 3 shows the results of the moderated mediation model for self-efficacy, where significant fibrosis ($\beta = 0.367$, $p < 0.001$) moderated the relationship between mental health and role-physical. The pick-a-point technique (Table 6) showed that the negative effects of mental health on role-physical were higher in patients who had significant fibrosis than in those who did not (absence of significant fibrosis, effect = 0.374, $p < 0.001$; presence of significant fibrosis, effect = 0.742, $p < 0.001$).

Table 7 presents the conditional indirect effects of passive/avoidance coping on self-efficacy through mental health and role-physical for the different levels of fibrosis. The results showed a larger conditional indirect effect on participants who had significant fibrosis than those who did not (absence of significant fibrosis, effect = −0.996, 95% CI = −1.675 to −0.445; presence of significant fibrosis, effect = −1.974, 95% CI = −3.257 to −0.895). In the pairwise comparisons between the conditional indirect effects, the bootstrapped 95% CI did not include 0, confirming that the mediation effect was moderated by fibrosis.

4. Discussion

It is not yet known what psychological biomarkers and clinical characteristics predict depressive symptoms and self-efficacy of NAFLD patients, which are relevant variables for therapeutic adherence by these patients, as recently demonstrated [16]. We therefore studied whether both variables were significantly associated with active coping, passive/avoidance coping, vitality, mental health, role-physical and BMI of the participants. We also wanted to find out whether there were any statistically significant differences in participants' depressive symptoms, active coping and vitality by absence or presence of T2DM, and also, whether there would be statistically significant differences in self-efficacy, passive/avoidance coping, mental health and role-physical by absence or presence of significant fibrosis. We examined whether vitality mediated the relationship between active coping and depressive symptoms, and whether there was a moderating effect of T2DM and BMI on this relationship. Finally, we analyzed whether the mental health and role-physical mediated the relationship between passive/avoidance coping and self-efficacy, and whether significant fibrosis moderated that relationship.

Our study had some limitations. For example, different liver or metabolic markers could have been included as moderators, such as lobulillar inflammation, hepatocellular ballooning or hypertension. Instead, we chose the variables in the literature which have been demonstrated to have more weight in the NAFLD biopsychosocial profile [2,3,9,32,33]. Another limitation was that cross-sectional mediation typically generate biased estimates of longitudinal parameters even when mediation is complete [34,35]. Moreover, due to the cross-sectional study design, it was not possible to establish causal relationships nor determine the long-term evolution of the results. For future studies a longitudinal study design would solve this problem and could reveal causal relationships between psychological and clinical variables, as well as identify changes in histological and metabolic features over time and their impact on patient's mental health and self-efficacy. Lastly, our sample consisted only of NAFLD patients, therefore our findings cannot be transferred to patients with other liver or metabolic diseases. However, the large size of the study sample, comprised of biopsied patients from real clinical practice in several Spanish hospitals, is the study's main strength and provides added value to the validity of the study results.

The results of the univariate analysis showed significant differences in depressive symptoms and self-efficacy of participants by age, gender, education, employment and fibrosis. Older participants, women, and participants with a low level of education, not actively employed and with significant fibrosis reported greater depression and less self-efficacy. Thus, the results of previous studies that have associated these characteristics with more depressive symptoms and poorer perceived self-efficacy in patients with chronic or metabolic liver pathologies [3,8,36–41] are confirmed.

Correlation analyses and comparison of means showed that active coping, vitality, T2DM and BMI were significantly associated with depressive symptoms, and mediation and moderated mediation analyses showed how they were interrelated. Vitality partially mediated the relationship between active coping and depressive symptoms. First, low

active coping predicted less vitality, in line with the association previously found between coping and quality of life in NAFLD [9]. Less vitality, in turn, was linked to worse depressive symptoms. These results highlight the need for a multidisciplinary NAFLD intervention model [15,42], including psychologists, who can implement cognitive-behavioral intervention techniques [43,44]. Patients would benefit from such intervention by overcoming risk factors associated with decline of their vitality and more depressive symptoms. Patient choice of coping strategies depends on how they construct their own experience with the disease [45]. Thus, less use of active coping strategies would be determined in large part by the patient's concept of the disease as an uncontrollable process that is beyond his/her own resources. Cognitive-behavioral intervention techniques, which have previously shown positive results with patients with chronic metabolic diseases [46], would help promote greater perception of the controllability of their disease. This would probably lead to more confidence in active coping strategies, such as positive reframing or acceptance of the problematic situation, as previously associated with better clinical outcomes and quality of life of T2DM patients [47]. And according to our results, this would indeed be linked to higher vitality and lower depressive symptoms of NAFLD patients. As fatigue and depression are the two main problems referred to by NAFLD patients [6,8], this is quite important. Another factor that could also be contributing to the link found between vitality and depressive symptoms is activation of immunological-inflammatory pathways [48]. Its relevance in the fatigue experienced both by the general population and patients with a diversity of chronic diseases has been demonstrated [49–51]. Furthermore, high serum levels of proinflammatory cytokines, such as interleukin (IL-6), have been associated with worse quality of life and more fatigue or lack of vitality through their effect on the central nervous system [52,53]. At the same time, IL-6 has been found to correlate positively with patient depressive symptoms [54]. Therefore, the action of inflammatory markers such as IL-6 could help interpret the close relationship between vitality and depressive symptoms in NAFLD patients, and should be addressed in future studies on their inclusion in pharmacological treatments for improving the physical and mental functioning of NAFLD patients.

Furthermore, the moderated mediation analyses revealed that T2DM and BMI moderated the relationship between active coping and depression through vitality. The indirect effects of vitality on depressive symptoms increased in patients with T2DM and higher BMI. That is, T2DM and obesity were associated with more negative impact of low vitality on depressive symptoms. Both metabolic pathologies, like NAFLD, are associated with decreased vitality [55,56]. Patients with T2DM commonly complain of less energy, mobility and ability to manage everyday situations [57]. These limitations are especially common in patients with microvascular or macrovascular complications [58]. Studies with long-term diabetics have also found their perceived social support unsatisfactory, and they may feel discriminated against by their immediate environment, even withdrawing from social life [57]. This is linked to the frequently intense emotional pressure related to the disease and its complications [59]. Thus, the inherent limitations of the disease and lack of social support may have contributed to the apparent negative effect of T2DM on the mental health of the NAFLD patients in our study. However, further studies are still needed to explore the influence of social support on depressive symptoms in these patients. Obesity is also related to poorer physical functioning, which may be explained by relaxation and sleep problems, and by their more impaired mobility and physical functioning [60]. Their lower vitality or energy is also linked to less physical activity [61], which in turn, is related to their heavier weight [62]. Inactivity, worse self-efficacy related to physical exercise, or fear and self-blame for weight gain could contribute to their poorer mental health [63–65]. Other factors commonly associated with obesity, such as oxidative stress, neuroinflammation or alterations in neurometabolism [66], could also contribute to the stronger negative impact on depressive symptoms of obese NAFLD patients. Our results suggest that metabolic comorbidity is a risk factor for the mental health of NAFLD patients, and they should therefore be considered vulnerable in healthcare screening. Diabetic and obese patients require special attention in intervention programmes that include among their objectives improving coping skills and quality of life. Some possibilities are T2DM and obesity education and self-management sessions, support groups, or problem-solving strategies are recommended. These techniques should be combined in an integrated intervention for the holistic management of NAFLD and metabolic comorbidity as two closely related conditions.

In another area, correlation analyses and comparison of means showed that passive/avoidance coping, mental health, role-physical and significant fibrosis were significantly associated with self-efficacy. Mediation and moderated mediation analyses showed how these variables were interrelated. The mental health and role-physical mediated partially in the relationship between passive/avoidance coping and self-efficacy. First, high passive/avoidance coping predicted worse mental health, which in turn, was associated with worse role-physical. Therefore, this finding suggests the relevance of coping in physical and mental quality of life of NAFLD patients [67]. Those patients who cope with their disease from a passive/avoidance style, employing strategies such as self-blame, self-distraction, behavioral disengagement or negation, would be expected to show worse psychological adjustment and greater presence of maladaptive health behaviors, anxiety and depressive symptoms, which is correlated with impaired quality of life [68]. This impact would be mainly on the mental sphere [9], which in turn would be associated with an impairment of the patient's role-physical, that is, perception of autonomy and ability to performing daily activities. This link between state of mental and physical health, which had already been previously proven in patients with metabolic syndrome [69], predicted participant self-efficacy, such that worse mental health and worse role-physical were associated with lower self-efficacy. Therefore, this study identified an at-risk psychological profile for self-efficacy in NAFLD, which is relevant considering that these patients refer to less confidence in managing their disease and making changes in health-related behavior than other chronic liver disease patients [70]. To date, there has been consensus in conceiving self-efficacy as a predictor of quality of life in a diversity of chronic pathologies [71–73]. However, the results of this study suggest that this could be a two-way relationship, since worse mental health and worse role-physical was associated with lower perception of self-efficacy. Implementation of cognitive-behavioral intervention techniques could help NAFLD patients cope, thereby improving their quality of life and self-efficacy. NAFLD psychoeducation to promote its acceptance, cognitive restructuring to modify maladaptive thought patterns associated with avoidance or self-blame, or relaxation, breathing or meditation techniques could all help NAFLD patients manage their physical and emotional limitations. Thus, more adaptive resources for analyzing, interpreting and removing obstacles derived from their disease and treatment, would enable them to progress from passive/avoidance to active coping, and improve their self-efficacy and physical and mental health.

Finally, moderated mediation analyses revealed that fibrosis moderated the relationship between passive/avoidance coping and self-efficacy through mental health and role-physical. The indirect effects of mental health on role-physical and consequently, on self-efficacy, was higher in patients with significant fibrosis. Significant fibrosis has previously been associated with worse physical and mental health in NAFLD [3]. This could be due to fatigue, which has previously been found in a higher proportion of patients with significant fibrosis, and its associated symptoms: mood alterations, including depression, daytime somnolence and cognitive dysfunction [74,75]. Thus, the presence of an at-risk psychological profile based on more maladaptive coping and

worse mental health would be linked to lower perceived productivity and functioning in daily activities, and worse self-efficacy, especially in patients with significant fibrosis. Our study suggests that fibrosis may play a determinant role in the biopsychosocial profile of NAFLD patients, and significant fibrosis would be a specific risk factor for self-efficacy. In light of all of the above physical and emotional limitations associated with liver fibrosis, psychological assessment and intervention for these patients should be given high priority.

In conclusion, this study found some psychological biomarkers and clinical characteristics that could predict depressive symptoms and self-efficacy in NAFLD patients. First, vitality mediates the relationship between active coping and depressive symptomatology, with T2DM and obesity as moderators. Metabolic comorbidity is associated with more negative effects of less active coping, and less vitality on depression. Second, the mental health and role-physical mediate the relationship between passive/avoidance coping and self-efficacy, moderated by fibrosis. The presence of significant fibrosis is linked to higher negative effects of more maladaptive coping and worse mental health on the patient's role-physical, and thereby, self-efficacy. The results of this study emphasize the importance of incorporating emotional and cognitive aspects, including cognitive-behavioral strategies, in NAFLD evaluation and treatment. Given the absence of effective pharmacological treatments for NAFLD [76] and the importance of depressive symptoms and self-efficacy in the therapeutic adherence of these patients [16], both psychological biomarkers should be two major psychological targets in future multinational treatment-effectiveness and intervention studies. The significant effects of coping, vitality, mental health or role-physical on depressive symptoms and self-efficacy, as well as the impact of metabolic comorbidity and fibrosis found in this study, should be given special consideration. This is particularly important given the alarming rate of non-adherence to therapy usually observed in these patients and the growing economic and clinical implications of this disease worldwide [15,77].

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Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jesús Funuyet-Salas, María Ángeles Pérez-San-Gregorio, Agustín Martín-Rodríguez and Manuel Romero-Gómez. The first draft of the manuscript was written by Jesús Funuyet-Salas and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

The authors have no competing interests to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2022.111045.

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