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# Anxiety and depression among Black breast cancer survivors: Examining the role of patient-provider communication and cultural values

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# Abstract

**Objective:** Breast cancer survivors frequently experience anxiety and depression post-treatment. Patient-provider communication and cultural values may impact these psychological outcomes. We examined the impact of patient-provider communication and cultural values on anxiety and depression among Black breast cancer survivors.

**Methods:** Using an observational, cross-sectional design, 351 survivors self-reported patientprovider communication (quality, confidence), cultural values (religiosity, collectivism, future time orientation), anxiety, and depression. Patients were categorized into high, moderate, and low levels of communication and cultural values. Separate linear regressions examined the effect of levels of communication and cultural values on anxiety and depression, controlling for sociodemographic variables.

**Results:** A subset of breast cancer survivors reported clinically significant symptoms of anxiety (40%) and depression (20%). Communication was associated with anxiety ( $\beta = -0.14$ , p = 0.01) and depression ( $\beta = -0.10$ , p = 0.04). Specifically, women reporting higher levels of communication quality/confidence reported lower levels of anxiety and depression. There was a trend towards a significant association between cultural values and depression ( $\beta = -0.09$ , p = 0.06).

Conflict of Interest

Appendix A. Supporting information

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The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Paige W. Lake: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft. Claire C. Conley: Conceptualization, Methodology, Writing – original draft. Tuya Pal: Funding acquisition, Investigation, Writing – review & editing. Steven K. Sutton: Methodology, Supervision, Writing – review & editing. Susan T. Vadaparampil: Conceptualization, Funding acquisition, Investigation, Supervision, Writing – review & editing.

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**Conclusions:** Black breast cancer survivors experience poor psychological functioning. Effective patient-provider communication may reduce anxiety and depression post-treatment.

**Practice implications:** Patient-provider relationships and patient empowerment may be key components of cancer survivorship. Special attention should be paid to patient-centered communication for Black breast cancer survivors.

### Keywords

Anxiety; Breast cancer; Culture; Depression; Patient-provider communication; Psychological symptoms; Values

# 1. Introduction

Breast cancer patients often experience anxiety and depression throughout the survivorship trajectory, including diagnosis, during treatment, and in the year post-treatment [1–3]. For the majority, symptoms recede [4]; for others, especially those with a prior history of anxiety or mood disorders, symptoms may persist or may reemerge after an initial decline [5–7]. Anxiety and depression are associated with poor health-related quality of life [8,9], reduced adherence to treatment and recommended follow-up care [10–12], and elevated risk of disease progression and death [13–15]. Thus, screening for and treating symptoms of anxiety and depression among cancer survivors is crucial [16].

However, most data on anxiety and depression after breast cancer come from samples of primarily White women [17]. Anxiety and depression are understudied among Black breast cancer survivors, particularly those who are diagnosed at a younger age [18]. Psychosocial concerns may differ for Black women, who are more likely to be diagnosed at an early age [19], have triple-negative breast cancer [20, 21], experience greater breast cancer morbidity and mortality [22,23], and report worse health-related quality of life [24,25].

Identifying predictors of anxiety and depression among Black breast cancer survivors is an important first step towards developing effective interventions to prevent or treat these symptoms. Prior research has examined the impact of patient-provider communication quality on psychosocial outcomes among cancer patients [26]. Provider communication techniques such as patient engagement, shared decision making, and relationship building during cancer care have been associated with reduced hopelessness, fear of cancer recurrence, and uncertainty about prognosis [27,28]. Many patients undergoing breast cancer treatment also view their providers as a source of emotional support [29]. Perceptions of provider communication and patient confidence in communicating with their providers can improve health-related quality of life among breast cancer survivors [8,30] and patients who are not satisfied with provider communication often subsequently experience increased worry about their future health [31].

The primary objective of this study was to examine the association between patient-provider communication on psychological symptoms (anxiety and depression) among Black breast cancer survivors. We hypothesized that survivors reporting higher communication quality and higher self-efficacy for patient-provider communication would have lower levels of

anxiety and depressive symptoms. As racial identity and meaning vary among group members [32], we also explored the relationship between patient cultural values (religiosity, collectivism, and future time orientation) and psychological symptoms.

# 2. Methods

#### 2.1. Procedures and participants

An observational, cross-sectional design was used. This study adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (see Appendix A). Data for the present study come from participants in a parent study that investigated genetic and lifestyle determinants of triple negative breast cancer in premenopausal Black women [33,34]. All procedures were approved by the University of South Florida (104559) and the Florida Department of Health (DOH H11168) Institutional Review Boards. Recruitment methods and participation are detailed elsewhere [33,34]. Briefly, Black women ages 50 diagnosed with invasive breast cancer from 2009 to 2012 were recruited from the Florida Cancer Data System (FCDS). Inclusion criteria for study participation were: (1) being a Florida resident when diagnosed with breast cancer between 2009 and 2012; (2) self-identifying as Black or African American; (3) English speaking; (4) diagnosed at or below age 50; (5) and alive at the time of recruitment. Exclusion criteria were: (1) non-Florida resident when diagnosed with breast cancer; (2) individuals who did not selfidentify as Black or African American; (3) non-English speaking; (4) and those diagnosed with breast cancer above age 50. FCDS released patient contact information and available clinical and sociodemographic information on all eligible participants. The lag time between diagnosis and availability of contact information from FCDS ranged from 6 to 18 months.

Eligible participants were contacted by mail, with follow-up contact via phone for nonresponders. In those willing to participate, written informed consent was obtained via mail. Study participation included completion of study questionnaires at three time points; the present study presents data from the baseline survey only.

#### 2.2. Measures

**2.2.1. Demographic characteristics**—Participants reported their age at the time of the baseline survey, education level, employment status, and partner status.

**2.2.2. General health status**—Participants rated their subjective health on a scale from 0 ("poor") to 4 ("excellent").

**2.2.3.** Cancer-related medical factors—Cancer stage at diagnosis was obtained from FCDS.

**2.2.4. Cultural values**—The African American Women's Cultural Beliefs Scale [35] assessed three cultural constructs prevalent in urban African American women: (1) *religiosity*, which includes church attendance, prayer, participation in religious ceremonies, spirituality, and beliefs about God as causal agents; (2) *collectivism*, the belief that the basic unit of society is the family rather than the individual; and (3) *future time orientation*, a person's tendency to think and act according to distal (i.e., future) consequences. Items are

measured on a four-point Likert scale (1 =strongly agree, 4 =strongly disagree). Items are averaged to create subscale scores that range from 1 to 4, with higher scores indicating greater endorsement of these constructs.

Preliminary analyses revealed rather extreme distributions for the individual subscales and covariation among subscales that encouraged creation of a single index of cultural values. Therefore, religiosity, collectivism, and future time orientation were combined to create a single variable representing an overall level of these combined characteristics ranging from 0 to 3. Table 1 presents the rules used to create the levels. First, participants were categorized as "high" (4, maximum score) or "low" (<4) on religiosity and collectivism; as well as "high" or "low" on future time orientation using a median split (3 = "high", <3 = "low"). *Level of cultural values* was scored 3 if "high" on all three cultural values subscales, 2 if "high" on two of three cultural values subscales, 1 if "high" on one of three, and 0 if "low" on all three.

**2.2.5. Patient-provider communication**—Two scales were used: (1) *Communication quality*. The Interpersonal Processes of Care Survey Short Form evaluated participant perceptions of communication with their provider [36]. Four items were measured on a five-point Likert scale (0 = never, 4 = always), with higher scores indicating more positive perceptions of patient-provider communication. Items were summed to create total scores ranging from 0 to 16. (2) *Self-efficacy*. The Perceived Efficacy in Patient-Provider Interactions scale assessed patient self-efficacy in obtaining medical information from their provider [37]. Nine items were measured on a five-point Likert scale (0 = not at all confident, 4 = very confident), with higher scores indicating greater perceived self-efficacy in communicating with providers. Items were summed to create total scores ranging from 0 to 36.

Again, preliminary analyses revealed extreme distributions for the communication measures and covariation between them that encouraged creation of a single index of communication. Thus, communication quality and self-efficacy were combined to create a variable representing patient-provider communication ranging from 0 to 2 (see Table 1). First, participants were categorized as "high" (16) or "low" (<16) on communication quality. Second, participants were categorized as "high" (36) or "low" (<36) on self-efficacy. Finally, participants were scored based on *level of communication*: 2 if "high" for both quality and self-efficacy, 1 if "high" for one, and 0 if "low" for both.

**2.2.6. Psychological symptoms**—The 14-item Hospital Anxiety and Depression Scale (HADS) [38] was used to measure *anxiety* (7-items) and *depression* (7-items). HADS was designed for use in non-psychiatric hospital settings and contains no questions referring to physical complaints to avoid confounding from underlying somatic diseases [38]. Participants rate items on a 4-point Likert scale (0–3), and items are summed for subscale scores ranging from 0 to 21. Higher scores indicate greater symptomatology, and the recommended clinical cutoff for each subscale is 8 [38].

### 2.3. Analytic strategy

All analyses were conducted using IBM SPSS version 25; statistical significance was specified at  $\alpha = 0.05$  (two-tailed), and cases with missing data were removed listwise. A priori power analyses were conducted for the parent study to determine adequate sample size; for the parent study, a sample size of 600 was determined to detect significant effects [33,34]. For the present analyses, post-hoc sensitivity analyses conducted in G\*Power [39] demonstrated 80% power to detect a small-to-medium effect size of  $f^2 = 0.04$  using linear multiple regression with 6 predictors,  $\alpha = 0.05$ , and N = 351. Descriptive statistics were used to characterize the sample. We planned to include any demographic variables (age, education, employment status, partner status) and clinical variables (health status, cancer stage) that significantly correlated with communication, cultural values, or outcomes of interest (anxiety and depression) in subsequent analyses.

All demographic variables were dichotomized, except for cancer stage. Spearman rank order correlations examined the relationship between demographic variables and psychological symptoms (anxiety and depression). Chi-square tests examined differences in demographic characteristics by communication group and cultural values group.

Finally, two multivariable regression models examined the significance of the association between communication and cultural values and anxiety and depression.

# 3. Results

#### 3.1. Preliminary and descriptive analyses

Of the 1647 eligible women with breast cancer in FCDS, we established contact with 882. Of these, 480 consented to participate in the parent study (54%) of which 380 (43%) consented to participate in the current study, which entailed completing additional measures of cultural values, patient-provider communication, and psychological functioning (e.g., anxiety, depression).

Sociodemographic characteristics by level of communication and cultural values are provided in Table 2. On average, participants were 44 years of age, 40% had a college degree or more, 63% were employed full-time, and 39% were partnered. At the time of study participation, women were on average 1.2 years post-diagnosis. The majority (51%) were diagnosed with localized breast cancer.

Employment, health status, and education level were significantly correlated with psychological symptoms (all *p*'s < 0.05, see Table 3) and were included as control variables in multivariable analysis. Partner status significantly differed by communication group ( $\chi^2(2) = 6.78$ , *p* < 0.05), such that more women in the "poor communicators" group were partnered, compared to the "fair communicators" and "effective communicators" groups (see Table 2). Thus, we included partner status as a control variable in multivariable analysis. Communication groups and cultural values groups were equivalent on all other demographic and clinical variables.

The average HADS anxiety score was 6.7 (*SD*=4.4), and the average HADS depression score was 4.4 (*SD*=3.9). Thus, average anxiety and depression scores were below the clinical cut-off for symptoms (i.e., subscale scores 8). However, a subset of participants reported clinically significant symptoms of anxiety (n = 140, 40%) and depression (n = 70, 20%).

#### 3.2. Multivariable analyses

Table 4 presents the results for all variables in the multivariable model for anxiety and for depression. In multivariable analyses, level of communication was significantly associated with anxiety ( $\beta = -0.135$ , p = 0.01) and depression ( $\beta = -0.103$ , p = 0.04) while controlling for education, employment status, partner status, and health status. Specifically, women with higher communication scores reported lower levels of anxiety and depression. Level of cultural values demonstrated a marginally significant association with depression (p = 0.06), but not anxiety (p = 0.65).

# 4. Discussion and conclusion

#### 4.1. Discussion

Despite documented disparities in quality of life [24,25], Black breast cancer survivors are underrepresented in studies of psychological functioning after cancer [18]. To fill this gap, the present study examined the relationship between patient-provider communication (confidence in communicating with providers, perceptions of provider communication quality) and psychological symptoms (anxiety and depression) among Black breast cancer survivors.

Our results demonstrate that a subset of Black breast cancer survivors experience clinically significant levels of anxiety and depression post-treatment. Although prior studies have demonstrated that cancer survivors who identify as racial/ethnic minorities often experience poorer psychological functioning than non-Hispanic White cancer survivors [40,41], our sample of Black breast cancer survivors demonstrated rates of clinically significant anxiety (40%) and depression (20%) that are similar to those previously reported in majority White samples (anxiety: 9–48%; depression: 13–27%) [42–45]. However, estimated prevalence of anxiety and depression in cancer survivors varies based on the measure used to assess symptoms [44] and the time point at which symptoms are assessed [4]. Thus, methodological differences may limit direct comparisons between our sample and the prior literature.

While racially comparative studies have merit, within-group research is needed to understand the survivorship experiences of Black breast cancer survivors [46]. In our sample of Black breast cancer survivors, quality of and self-efficacy for patient-provider communication is associated with symptoms of anxiety and depression. This information can help inform interventions aiming to improve psychosocial outcomes among Black breast cancer survivors.

Consistent with our hypothesis, Black breast cancer patients in our study who reported positive perceptions of provider communication (i.e., endorsing that doctors or health professionals "really find out what [my] concerns were", "clearly explain their advice and

recommendations", etc.) and reported greater self-efficacy in communicating with their provider (i.e., endorsing confidence in their ability to "get a doctor to pay attention to what [I] have to say", "explain [my] chief health concern to a doctor", etc.) demonstrated lower levels of depression and anxiety. This aligns with previous findings from samples primarily consisting of White women (e.g., [30]).

There are several potential pathways by which patient-provider communication can influence health outcomes [28]. First, more effective patient-provider communication may increase the likelihood that one's health concerns are addressed. For example, a patient with high self-efficacy for patient-provider communication may be more likely to disclose symptoms of anxiety and depression to her provider, and thus receive treatment for psychological symptoms. However, the data in the present study are cross-sectional, which precludes assumptions about directionality. Alternatively, it is possible that patients with higher symptoms of anxiety and depression perceive worse communication with their providers. In one study of 703 outpatients with coronary heart disease, depressive symptoms were associated with perceived deficits in patient-provider communication after adjusting for demographic factors, medical comorbidities, and disease severity [47]. Specifically, an increase in patient depressive symptoms by one standard deviation was associated with 50% greater odds of reporting poor explanations of the medical condition, and 30% greater odds of reporting poor provider responsiveness to patient preferences. Similarly, in a study of patient-provider visits of 406 persons with HIV, patients reporting more depressive symptoms felt less respected and were less likely to report that their provider knows them as a person than patients reporting none/mild depressive symptoms [48]. Thus, additional, longitudinal studies are needed to disentangle the complex relationship between patient-provider communication and psychological symptoms among Black breast cancer survivors.

The deleterious effects of poor patient-provider communication are particularly critical to address, given that previous research has found that Black breast cancer patients report poorer perceptions of provider communication than other racial/ethnic groups [49,50]. These findings may be rooted in provider implicit racial bias (i.e., racial attitudes and stereotypes that are activated spontaneously) [51,52]. Provider implicit racial bias is negatively associated with care satisfaction and provider trust among racial/ethnic minority patients [53]. In turn, satisfaction and trust predict of numerous health outcomes for both the population at large [54] and cancer patients specifically [55]. Given the shortage of Black oncologists in the United States [56], Black breast cancer survivors are likely to see an oncologist of a different race/ethnicity. For this reason, special attention should be paid to the role of provider implicit racial bias in cancer survivorship care. Culturally competent patient-provider communication may improve psychosocial outcomes in patients diagnosed with cancer [57].

This study also explored the relationship between cultural values and psychological symptoms; however, cultural values were not related to anxiety or depression. To our knowledge, one other study has examined the relationship between cultural values and psychosocial outcomes: Sheppard and colleagues [58] found that religiosity, collectivism, and Afrocentric worldview were highly endorsed by Black women with breast cancer,

but these variables did not significantly predict anxiety or depression in multivariable models that controlled for demographics, socioeconomic status, and process of care factors (e.g., healthcare barriers, patient satisfaction). They concluded that cultural values may mediate or moderate anxiety or depression, rather than having a direct effect on psychological symptoms [58]. In addition, it is possible that previously observed disparities in psychosocial outcomes after cancer are not a function of internal cultural identity, and are instead attributable to social determinants of health, including structural racism [59]. Given that structural racism is associated with racial differences in socioeconomic status, and in turn, negative health outcomes, future research could explore anti-racism training in medical education and/or continuing education as one option to buffer the impact of provider implicit bias on psychosocial outcomes among Black breast cancer patients [60]. Future research should also use a social determinants of health framework to examine disparities in survivorship outcomes for Black breast cancer survivors.

Study strengths include the statewide recruitment of individuals across a variety of institutions, enhancing generalizability to community-based cancer survivors in Florida, rather than only those who seek care at large, academic medical centers. Our sample was also diverse in terms of participant socioeconomic status and health status. In addition, our study provides further insight into perceptions of provider communication and patient confidence in communication abilities among Black breast cancer patients, a patient population that has historically experienced discrimination in healthcare. Our findings can be utilized to develop patient-centered interventions that specifically target minority cancer patients. Finally, our focus on Black breast cancer survivors specifically, rather than a racially comparative framework, allows for in-depth examination of the experiences of this group [46], which is historically underrepresented in cancer survivorship research.

Nonetheless, the results of the present study should be interpreted in light of some limitations. First, results may be subject to selection bias as only 54% of the women with whom contact was established consented to participate. Second, patient-provider communication, cultural values, and psychosocial outcomes were collected via self-report and may be subject to demand characteristics and social desirability. Third, the crosssectional design obviates causal conclusions regarding the relationships observed. Fourth, multivariable linear regression models explained only 10% of the variance in anxiety and 16% of the variance in depression. Additional variables that were not assessed in the present study – such as social support, cancer symptoms and side effects, and personal beliefs (e.g., optimism, locus of control) - are likely to contribute to variance in anxiety and depression symptoms. Finally, we elected to dichotomize communication and cultural values variables in the present analyses. While dichotomizing addresses the extremely skewed distributions observed for these variables, it may lead to restricted variability and loss of precision [61,62]. Future studies might purposively sample individuals with values spanning the possible range of communication and cultural values, enabling use of continuous variables in subsequent analyses.

#### 4.2. Conclusion

This study attempts to shed light on the relationship between patient-provider communication and psychosocial outcomes among Black cancer survivors. Overall, Black breast cancer survivors had low anxiety and depression post-treatment. However, a subset reported clinically significant symptoms of anxiety and depression. Consistent with findings from samples primarily consisting of non-Hispanic White cancer survivors, greater provider communication quality and higher patient self-efficacy for communication were associated with decreased levels of depression and anxiety among Black breast cancer survivors. Thus, effective patient-provider communication may reduce Black breast cancer patients' anxiety and depression post-treatment, in turn reducing disparities in psychosocial outcomes in cancer survivorship.

#### 4.3. Practice implications

Given the impact of communication quality and self-efficacy on anxiety and depression, patient-provider relationships and patient empowerment may be key components of cancer survivorship. Practice changes may be needed to support high-quality communication between Black breast cancer patients and their providers. Multilevel interventions targeting both patients and providers may be needed in order to demonstrate meaningful improvements in patient-provider communication.

For providers, interventions might focus on improving patient-centered communication skills, including patient engagement, shared decision making, and relationship building. Given the potential role of racial implicit bias in providers' interactions with Black breast cancer survivors, implicit bias training should also be considered. Provider training could be stand-alone (i.e., a continuing education model) or incorporated into medical education.

For patients, interventions might focus on increasing self-efficacy in communicating with providers. Patient-directed interventions such as question prompt lists and individualized communication coaching may result in downstream improvements in anxiety and depression, particularly if paired with provider training.

# Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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# Data availability

Data will be made available upon reasonable request to the corresponding author (S.T.V.).

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# Table 1

Scoring for communication and cultural beliefs variables.

Variable	Range	High	Low	Overall
Communication Variables				2 "highs" =
Communication quality	0–16	16	< 16	Effective
Confidence in communication	0–36	36	< 36	1 "high" = Fair 0 "highs" = Low
African American Cultural Variables				3 "highs" = High 2 "highs" =
Religiosity	1–4	4	< 4	Moderate
Collectivism	1 –4	4	< 4	1 "high" = Low
Future time orientation	1 –4	3	< 3	0 "highs" = Minimal

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# Table 2

Demographic characteristics of Black breast cancer patients by level of communication and cultural values (n = 352).

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	Level of Comm	Inication			Level of Cultural V	Values			
	Poor(n = 190)	Fair (n = 102)	Good $(n = 60)$	d	Minimal (n = 81)	Low $(n = 130)$	Moderate $(n = 91)$	High (n = 49)	d
Age (years): M(SD)	44 (6.6)	42.8 (6.7)	44.9 (5.5)	0.12	42.8 (6.6)	43.8 (7.1)	44.7 (5.5)	44 (6.3)	0.28
Education: college graduate (n, %)	78 (41.1)	41 (40.2)	19 (31.7)	0.42	31 (38.3)	50 (38.5)	40 (43.9)	16 (32.7)	0.61
Employment status: employed (n, %)	111 (58.4)	72 (71.8)	37 (62.6)	0.12	51 (63.0)	86 (66.2)	57 (62.6)	25 (51.0)	0.32
Partner status: partnered (n, %)	85 (44.7)	33 (32.4)	18 (30.0)	$0.03^{*}$	34 (42.0)	47 (36.4)	34 (37.4)	21 (42.9)	0.79
Health status: poor/fair (n, %)	118 (62.1)	60 (58.8)	27 (45.0)	0.06	53 (65.4)	78 (60)	51 (56.0)	23 (47.3)	0.20
Cancer stage (n, %)				0.23					0.64
Localized	100 (52.6)	57 (55.9)	28 (46.7)		39 (48.1)	74 (56.9)	45 (49.4)	26 (53.1)	
Regional	83 (43.7)	40 (39.2)	24 (40.0)		37 (45.7)	49 (37.7)	40 (43.9)	21 (42.9)	
Distant	5 (2.6)	4 (3.9)	6(10.0)		5 (6.2)	5 (3.8)	5 (5.4)	0 (0.0)	
Unstaged	3 (1.6)	1 (0.9)	2 (3.3)		1 (12)	2 (1.5)	1 (1.1)	2 (4.1)	
* significant at p < 0.05									

#### Table 3

Correlations between sociodemographic factors and psychosocial outcomes (n = 352).

Measure	Depression	Anxiety
Age	0.07	-0.23
Education level	-0.22 **	-0.13 *
Employment status	-0.15 *	0.13*
Partner status	0.04	0.02
Health status	-0.31 **	-0.23 **
Cancer stage	0.02	0.05

\* significant at p < 0.05

\*\* significant at p < 0.001

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Table 4

Multivariable predictors of psychosocial outcomes.

	Unstandardized Coefficient (SE)	đ	95% CI	d	$\mathbb{R}^2$
Model 1: Anxiety					0.099
Level of communication $^*$	-0.79 (0.31)	-0.14	(-1.40 to -0.18)	0.012	
Level of cultural values	-0.11 (0.24)	-0.02	(-0.58 to 0.36)	0.65	
Education level $^*$	-1.11 (0.48)	-0.12	(-2.06 to -0.16)	0.02	
Employment status	-0.73 (0.49)	-0.08	(-1.69 to 0.23)	0.13	
Partner status	0.09 (0.47)	0.01	(-0.84 to 1.02)	0.85	
Health status **	-1.76 (0.47)	-0.20	(- 2.68 to - 0.83)	0.001	
<b>Model 2: Depression</b>					0.156
Level of communication $^*$	-0.53 $(0.26)$	-0.10	(-1.04 to -0.01)	0.04	
Level of cultural values	-0.37 (0.20)	-0.09	(-0.77 to 0.03)	0.06	
Education level **	-1.32 (0.41)	-0.17	(-2.12 to -0.51)	0.001	
Employment status	-0.69(0.41)	-0.09	(-1.50 to 0.12)	0.09	
Partner status	0.06 (0.40)	0.01	(-0.73 to 0.84)	0.88	
Health status **	-2.06 (0.40)	-0.26	(-2.84 to -1.27)	0.001	
* significant at $p < 0.05$					
** cionificont of a < 0 001					
Significant at $p < 0.001$					