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ASSOCIATION OF ANXIETY AND DEPRESSION WITH PULMONARY-SPECIFIC SYMPTOMS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE*

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Abstract

Objectives—To examine the association of anxiety and depression with pulmonary-specific symptoms of Chronic Obstructive Pulmonary Disease (COPD), and to determine the extent to which disease severity and functional capacity modify this association.

Method—Patients (*N* = 162) enrolled in the INSPIRE-II study, an ongoing randomized, clinical trial of COPD patients and their caregivers who received either telephone-based coping skills training or education and symptom monitoring. Patients completed a psychosocial test battery

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including: Brief Fatigue Inventory, St. George's Respiratory Questionnaire, UCSD Shortness of Breath Questionnaire, State-Trait Anxiety Inventory, and Beck Depression Inventory. Measures of disease severity and functional capacity (i.e., FEV_1 and six-minute walk test) were also obtained.

Results—After covariate adjustment, higher anxiety and depression levels were associated with greater fatigue levels (*p*s < .001, ΔR^2 = 0.16 and 0.29, respectively), shortness of breath (*p*s < .001, ΔR^2 = 0.12 and 0.10), and frequency of COPD symptoms (*p*s < .001, ΔR^2 = 0.11 and 0.13). In addition, functional capacity was a moderator of anxiety and pulmonary-specific COPD symptoms. The association between anxiety and shortness of breath ($p = 0.009$) and frequency of COPD symptoms ($p = 0.02$) was greater among patients with lower functional capacity.

Conclusions—Anxiety and depression were associated with higher levels of fatigue, shortness of breath, and frequency of COPD symptoms. It is important for clinicians to be aware of the presence of anxiety and depression in COPD patients, which appears to correlate with pulmonary-specific COPD symptoms, especially in patients with lower functional capacity. Prospective design studies are needed to elucidate the causal relationships between anxiety and depression and pulmonary-specific symptoms in COPD patients.

Keywords

anxiety; depression; COPD

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a progressive airway disease marked by symptoms of dyspnea, sputum production, wheezing, coughing, chest tightness, and fatigue [1]. The morbidity associated with these symptoms is substantial as patients often report a significant degree of disability and restriction in daily activities, decreased quality of life, and psychological distress [2]. Not surprisingly, two of the most common co-morbidities in COPD are anxiety and depression [3]. Prevalence rates of elevated depressive symptoms have been reported to be as high as 80% [4–6] and rates of elevated anxiety symptoms may exceed 90% [5, 7]. The presence of anxiety and depression in COPD is also associated with increased COPD exacerbations, COPD-related hospitalizations, and mortality [6]. Despite their negative influence on quality of life and medical outcomes [3], anxiety and depression often go undetected in clinical practice due to variations in the frequency and type of diagnostic assessment, variability in clinical presentation, and the significant overlap between co-morbid pulmonary symptoms [7].

In recent years, there has been a growing literature on the impact of psychological distress on medical factors such as pulmonary function, exercise capacity, and pulmonary-specific symptoms of COPD [8–11]. Several studies have now shown an association between elevated levels of depression and greater pulmonary symptoms (e.g., fatigue or dyspnea) [12–19]. Few studies have assessed the association between anxiety and pulmonary symptoms [15, 16] despite the complex, bidirectional relationship between anxiety and pulmonary-specific symptoms in COPD patients. Anxiety is often associated with exacerbated pulmonary symptoms such as coughing and dyspnea, which can also be potent stimuli for greater levels of anxiety [20, 21]. In addition, some therapies for COPD, such as

short-acting beta agonist medications, may increase symptoms of anxiety as a result of side effects [20].

Health status, including disease severity and functional capacity, may also modify the association between anxiety and depression and pulmonary-specific symptoms in COPD, yet research on this topic is limited [22, 23]. To date, no investigation has examined the association of functional capacity on symptoms of anxiety and depression in COPD. The primary aim of this study was to determine the association between anxiety and depression and pulmonary-specific symptoms within COPD patients. We also sought to examine disease severity and functional capacity as potential moderators of this association.

METHODS

Study Design

Participants were enrolled in the INSPIRE-II study [24], an ongoing randomized, clinical trial of COPD patients and their caregivers who received either telephone-based coping skills training or an education control condition. Eligibility requirements included ≥ 21 years of age, a diagnosis of COPD (i.e., $FEV_1/FVC < 70\%$; forced expiratory volume/forced vital capacity, which are standard measurements used in spirometry testing), $FEV_1 > 25\%$, and capacity to give informed consent and follow study procedures. Exclusion criteria included dementia, psychosis, acute suicide or homicide risk, other medical illnesses (e.g., cancer) that could likely cause death within 3 years, lack of ambulatory function, unstable angina, congestive heart failure (stage III or IV), and active involvement in a pulmonary rehabilitation or a formal exercise program. All patients provided written informed consent to participate. The consent form and all study procedures were approved by the institutional review board at Duke University Medical Center.

Procedure

Participants completed a psychosocial test battery that included self-reported measures of pulmonary-specific COPD symptoms, anxiety, and depression. Demographic, medical, disease severity, and functional capacity variables were also obtained including the six minute walk test (6MWT) and pulmonary functioning (i.e., forced expiratory volume; FEV_1 % predicted value).

Psychosocial Measures

Brief Fatigue Inventory (BFI) [25]—The BFI is a nine-item scale that measures the level of current, worst, and usual fatigue and interference due to fatigue. Respondents are asked to rate each item on a scale that ranges from 0 to 10. An average score from these nine items is calculated with scores (≥ 7) indicating clinically significant levels of fatigue [25].

St. George's Respiratory Questionnaire (SGRQ)–Symptom Component [26, 27]—The SGRQ is a standardized, disease-specific measure used to assess patients with mild to severe airway disease. The SGRQ consists of 50 items that produce three domain scores and one overall score measuring: symptoms, activities, and impact. The symptom component consists of eight items that assess the frequency over the last year of coughing,

sputum production, dyspnea, wheezing, and number of respiratory attacks. Responses to these items are rated on four or five possible levels of frequency of occurrence [26]. A higher score indicates a greater frequency of symptom occurrence.

University of California at San Diego Shortness of Breath Questionnaire (SOBQ) [28]—The SOBQ is a 24-item measure that assesses the occurrence of shortness of breath on a 6-point scale (0 to 5) during 21 activities of daily living associated with varying levels of exertion. The SOBQ items are summed with total scores ranging from 0 to 120 [28]. Higher scores indicate greater perceptions of dyspnea.

Beck Depression Inventory (BDI-II) [29]—The BDI-II is a standardized 21-item self-report questionnaire assessing symptoms and attitudes related to depression. The items are summed with total scores ranging from 0 to 63 with higher scores indicating higher levels of depression [29].

State-Trait Anxiety Inventory (STAI) [30]—The STAI consists of two separate self-report inventories, one measuring state anxiety and the other trait anxiety. The STAI was developed as a tool for investigating anxiety in normal (non-psychiatric) adults, but has been used in assessing anxiety in neuropsychiatric, medical, and surgical patients.

Demographic, Medical, Disease Severity, and Functional Capacity Variables

Demographics and medical characteristics were collected using self-report questionnaires that assessed age, gender, height, weight, ethnicity, marital status, education level, smoking status, medical comorbidities (as measured by the Charlson Comorbidity Index [31]), short-acting beta agonist medication usage, and anti-depressant and anxiolytic medication usage. Patients also performed the Six Minute Walk Test (6MWT), a self-paced, timed test of the total distance that a patient is able to walk in 6 minutes [32]. Further, patients also underwent standard spirometry testing according to the American Thoracic Society guidelines, which provided information on forced vital capacity and FEV_1 [33]. These measurements are useful in evaluating the severity of obstruction or the presence and severity of restrictive lung disease [33].

Data Analyses

Statistical analyses were conducted using SAS [34]. Models were examined for normality, skewedness, kurtosis, multicollinearity, and homoscedasticity of the residuals prior to analysis. Because fatigue was measured twice during this investigation (i.e., once using the BFI as an outcome measure and again as an item assessed on the BDI-II), a new variable was calculated for depression which excluded fatigue from the BDI-II. Use of this strategy minimized the overlapping measurement of fatigue since it could artificially inflate the likelihood of detecting a significant correlation between depression scores and BFI outcomes. The new depression variable, which excluded fatigue, was used in all regression analyses.

Hierarchical Regression Analyses—The primary data analysis strategy was to conduct separate hierarchical regression analysis models on the BFI, SOBQ, and SGRQ (Symptom

Component) scales. Each model was adjusted for age, gender, BMI, smoking status, FEV_1, medical comorbidities, 6MWT, short-acting beta agonist, anti-depressant, and anxiolytic medications. Following covariate adjustment, anxiety and depression symptoms were entered into the models separately.

Associations with Disease Severity and Functional Capacity—Hierarchical regression analyses with product terms were used to examine the associations of anxiety and depression on BFI, SOBQ, and SGRQ (Symptom Component) scales at varying levels of disease severity and functional capacity (i.e., 6MWT and FEV_1). Scores for anxiety, depression, 6MWT, and FEV_1 were mean-centered to enhance interpretation of model estimates. All models were adjusted for age, gender, BMI, smoking status, medical comorbidities, short-acting beta agonist, anti-depressant, and anxiolytic medication usage. Following covariate adjustment (Step 1), anxiety or depression main effects and 6MWT or FEV_1 main effects were entered into the models separately (Step 2), followed by corresponding product terms (e.g., anxiety by 6MWT; Step 3). A total of 12 models were constructed in order to test each product term separately.[1] In the presence of a significant interaction, simple slopes were generated to examine the effect of anxiety or depression symptoms on BFI, SOBQ, and SGRQ (Symptom Component) at one standard deviation above and below the centered mean of either 6MWT or FEV_1.

RESULTS

Participant Characteristics

One hundred sixty-two participants were included in this study. The mean age for the overall sample was 67 ± 8 years. As shown in Table 1, the majority of patients were Caucasian, married, and had at least a high school education. On average, participants were overweight [35], reported a history of lung disease for 3.8 ± 2 years, and had at least two comorbid medical conditions. Approximately 16% of participants were current smokers. The average FEV_1 (% predicted value) in the sample was 46.5% ± 17.1%, indicating that participants demonstrated moderate levels of pulmonary obstruction. Participants walked an average of 346 ± 106 feet during the six minute walk test, which is considered low based on age-adjusted normative data [36], suggesting a lower functional capacity level, consistent with their diagnosis of COPD. Approximately 53% of participants reported the use of short-acting beta agonist medications (e.g., albuterol). More than one-quarter of participants in our sample (27%) were taking anti-depressant medications and 12% were taking anxiolytic medications.

Anxiety, Depression, and COPD Symptoms

Approximately 27.8% of the sample had elevated levels of depressive symptoms according to the BDI-II (cut-score ≥ 14) [29] while 58% of participants endorsed medium to high levels of anxiety symptoms according to the STAI (cut-score ≥ 31) [30, 37].

[1]The authors recognize that conducting multiple tests could artificially inflate the Type I error rate. However, several analytic strategies were considered (e.g., MANCOVA) to address this potential problem and the study results remained the same regardless of the strategy used. As a result, the findings are described using hierarchical regression analyses in order to highlight the significant results for each outcome measure separately.

After covariate adjustment, main effects models demonstrated that higher reported levels of anxiety were associated with higher levels of fatigue (ΔR^2 = 36%; ΔF[1, 150] = 35.8, p < .0001) and shortness of breath (ΔR^2 = 12%; ΔF[1, 149] = 34.7, p < .0001), and greater frequency of COPD symptoms (ΔR^2 = 11%; ΔF[1, 150] = 22.9, p < .0001; Table 2).

Similarly, after covariate adjustment, main effects models showed that higher levels of depression were associated with higher levels of fatigue (ΔR^2 = 29%; ΔF[1, 150] = 77.6, p < .0001), shortness of breath (ΔR^2 = 10%; ΔF[1, 149] = 30.1, p < .0001), and greater frequency of COPD symptoms (ΔR^2 = 13%; ΔF[1, 150] = 29.2, p < .0001; Table 2).

Association of Functional Capacity on Anxiety, Depression, and COPD Symptoms

After adjustment for covariates, there was a significant anxiety by 6MWT interaction on shortness of breath (p = 0.009; ΔR^2 = 0.02). Figure 1(A) shows that the association between anxiety and shortness of breath was greater among patients with lower functional capacity compared to patients with higher functional capacity. Patients with low performance on the 6MWT and higher levels of anxiety were more likely to exhibit greater symptoms of shortness of breath.

Similarly, after covariate adjustment, there was a significant anxiety by 6MWT interaction on frequency of COPD symptoms (p = 0.02; ΔR^2 = 0.03). Figure 1(B) shows that higher levels of anxiety were associated with greater frequency of COPD symptoms at both high and low levels of functional capacity. At higher levels of anxiety, patients demonstrated more frequent COPD symptoms regardless of their level of functional capacity.

There was not a significant anxiety by 6MWT interaction on fatigue (p = .13). In addition, all depression by 6MWT interactions on fatigue (p = 0.19), shortness of breath (p = 0.20), and frequency of COPD symptoms (p = 0.55) were non-significant. Finally, FEV_1 did not affect the relationship between anxiety, depression, and COPD symptoms as all interactions between these variables were non-significant.

DISCUSSION

Higher levels of anxiety and depression are associated with elevated levels of pulmonary-specific symptoms among individuals with COPD, including fatigue, shortness of breath, and frequency of COPD symptoms. These associations remained significant even after adjustment for background characteristics and potential confounders, such as age, gender, BMI, smoking status, medical comorbidities, and short-acting beta agonist, anti-depressant, and anxiolytic medications. Although the causal direction of these findings cannot be determined, as heightened anxiety and depression could be a cause or consequence of elevated pulmonary symptoms, the results are consistent with several prior investigations that examined the association between higher depression scores and elevated levels of fatigue or dyspnea [12–14, 17–19]. However, unlike previous studies [15, 16], we examined the associations between *both* anxiety and depression across multiple measures of pulmonary symptoms. Demonstrating that both anxiety and depression were significantly related to pulmonary-specific COPD symptoms is clinically relevant as it reinforces the need to assess for these psychological comorbidities to improve pulmonary symptom

management and increase quality of life among patients [38]. Several studies have shown that pulmonary-specific COPD symptoms are predictive of outcomes such as increased risk of hospitalization [39], failure after treatment of exacerbations [40], and early mortality [41]. In this context, identifying and treating modifiable factors such as anxiety and depression could potentially result in improved COPD outcomes.

Another important finding from this study is that the strength of the association between anxiety and pulmonary-specific COPD symptoms appears to vary by functional capacity. The association of anxiety on shortness of breath and frequency of COPD symptoms was greater among patients who demonstrated lower functional capacity. However, at higher levels of anxiety, patients reported a greater frequency of COPD symptoms *regardless* of their functional capacity. The cross-sectional nature of this study did not allow us to determine if lower functional capacity increased anxiety symptoms or if anxiety symptoms reduced functional capacity. Nonetheless, it may be that identifying and treating anxiety in patients at earlier stages of COPD, particularly among individuals with lower functional capacity, could help to improve pulmonary-specific COPD symptom management. This is particularly important as nearly 60% of participants in our sample reported elevated levels of anxiety and more than 25% reported taking psychotropic medications.

To our knowledge, only two prior investigations have shown that disease severity (as measured by FEV_1) modifies the association between psychological distress and pulmonary-specific COPD symptoms [22, 23]. Balcells and colleagues [23] showed that the association between anxiety and depressive symptoms on health-related quality of life (as measured by the St. George's Respiratory Questionnaire) was stronger among patients with severe to very severe COPD than among those with mild to moderate COPD symptoms. In another study, Hajiro and colleagues [22] showed that anxiety was correlated with health-related quality of life only among patients with moderate to severe COPD symptoms. However, in contrast to these studies [22, 23], we did not find that FEV_1 modified the association between anxiety and pulmonary symptoms. This may suggest that COPD severity as measured by FEV_1 is not differentially related to anxiety or depressive symptoms. It could also be that our lack of findings are explained by the fact that patients were only included in this study if they had a $FEV_1 > 25\%$. The exclusion of patients with more severe COPD may have precluded our ability to observe a significant association between FEV_1, anxiety, and pulmonary symptoms.

Given that anxiety and depressive symptoms are both correlated to pulmonary-specific symptoms among patients with COPD and that functional capacity appears to moderate the association between anxiety and pulmonary symptoms, there is a need for treatments that reduce the anxiety characteristic of many COPD patients. Evidence is available for the efficacy of both pharmacological and non-pharmacological treatments of anxiety in COPD [38].

Limitations

The cross-sectional design of the study does not allow us to determine if a causal relationship between anxiety and depression and pulmonary-specific symptoms of COPD exists since increased anxiety and depression could be a cause or consequence of elevated

pulmonary symptoms among patients with COPD. The exclusion of patients with more severe COPD (i.e., $FEV_1 \leq 25\%$) may have precluded our ability to observe a relationship between FEV_1, anxiety, and pulmonary-specific symptoms. The extent to which FEV_1 impacts the relationship between anxiety and pulmonary symptoms among those with more severe COPD warrants further investigation.

CONCLUSIONS

Findings from this study suggest that co-morbid anxiety and depression are associated with increased fatigue, shortness of breath, and frequency of pulmonary-specific symptoms in COPD. The extent to which anxiety and depression exacerbate pulmonary symptoms could not be determined, as heightened anxiety and depression could be a cause or consequence of elevated pulmonary symptoms. Patients with low performance on the 6MWT and higher levels of anxiety were more likely to exhibit greater symptoms of shortness of breath. Furthermore, the association between increased anxiety and frequency of COPD symptoms appears to be strongest among patients with impaired functional capacity. At higher levels of anxiety, patients demonstrated more frequent COPD symptoms regardless of their level of functional capacity. A prospective design study is needed to better understand the temporal association between anxiety symptoms and functional capacity.

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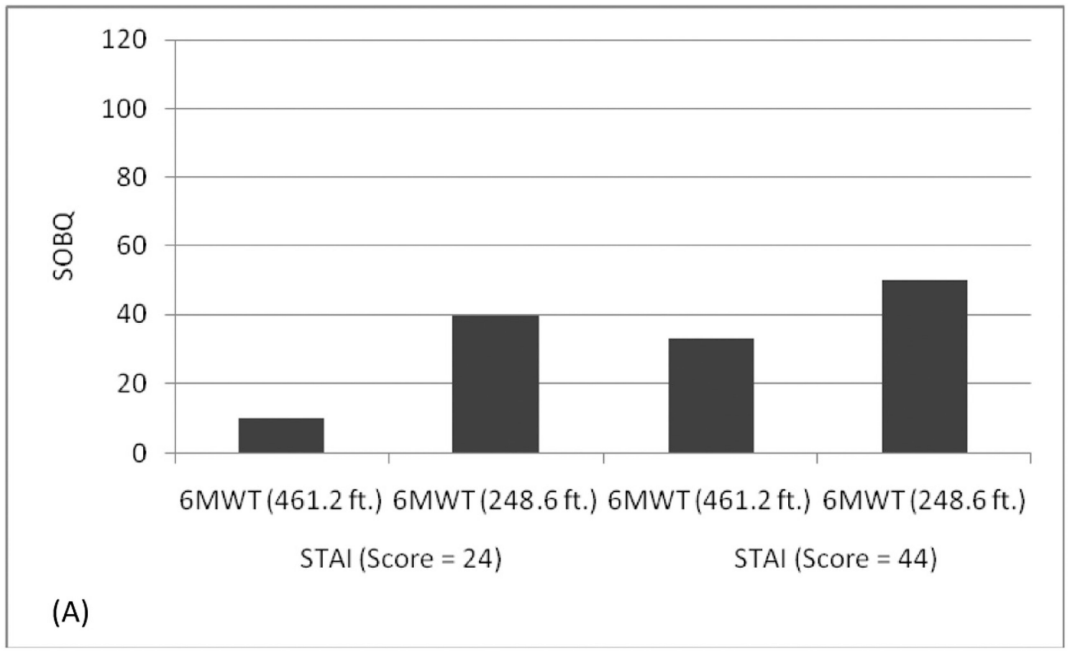

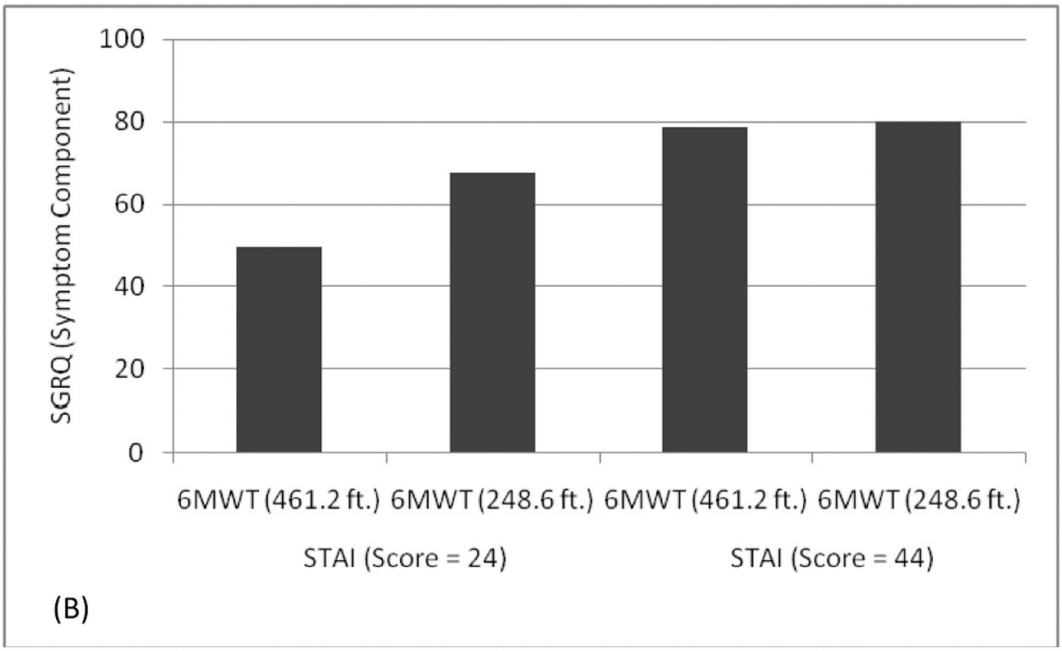

Figure 1.

Panel A – Association between High (+1 *SD*) and Low (−1 *SD*) Levels of Anxiety (STAI) and Shortness of Breath Questionnaire (SOBQ) at High (+1 *SD*) & Low (−1 *SD*) Levels of Functional Capacity (6MWT); Panel B – Association between High (+1 *SD*) and Low (−1 *SD*) Levels of Anxiety (STAI) and St. George's Respiratory Questionnaire (Symptom Component) at High (+1 *SD*) and Low (−1 *SD*) Levels of Functional Capacity (6MWT).

Table 1

Background Characteristics

Variable	Mean	*SD*
Age (years)	67.1	8.3
Men, *n* (%)	100 (61.7)	
BMI	28.9	6.4
Ethnicity, *n* (% Whites)	146 (90.1)	
Education, *n* (% beyond high school)	94 (58.0)	
Married, *n* (%)	105 (64.8)	
Lung disease duration (years)	3.8	2.1
Current smoker, *n* (%)	26 (16.0)	
CCI	2.1	1.7
6MWT – Total distance (in feet)	345.9	106.3
FEV_1 (% predicted value)	46.5	17.1
Short-acting beta agonist medication, *n* (%)	85 (52.5)	
Anti-depressant medication, *n* (%)	43 (26.5)	
Anxiolytic medication, *n* (%)	20 (12.3)	

Notes: Data are given as number (%) unless otherwise indicated. *SD* = standard deviation; BMI = Body Mass Index; CCI = Charlson Comorbidity Index; 6MWT = 6 Minute Walk Test; FEV_1 = Forced Expiratory Volume.

Table 2

Association of Anxiety and Depression with Pulmonary-Specific Symptoms of COPD

	Predictors					
	Anxiety			Depression		
Outcomes	***B***	***S.E.***	**β**	***B***	***S.E.***	**β**
Fatigue	0.10	0.02	0.43**	0.17	0.02	0.59**
Shortness of breath	0.81	0.14	0.36**	1.00	0.18	0.35**
COPD symptoms	0.88	0.18	0.35**	1.29	0.24	0.40**

** $p < .001$.