Family Support as a Mediator in the Relationship Between Sense of Coherence and Depression in Patients with COPD

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Article

Family Support as a Mediator in the Relationship Between Sense of Coherence and Depression in Patients with COPD

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Abstract

Chronic Obstructive Pulmonary Disease (COPD) is a progressive respiratory condition commonly caused by prolonged exposure to harmful particles or gases. The literature on COPD patients is rich in reports of psychological symptoms such as anxiety and depression, which often co-occur with the physical manifestations of the disease. The primary aim of this study was to investigate the role of the sense of coherence and family support in depressive symptomatology among patients with COPD. A total of 143 patients (107 men and 32 women) participated, completing the Beck Depression Inventory (BDI), the Sense of Coherence-13 scale (SOC), and the Family Support Scale (FSS). Among the participants, 46.8% exhibited no depressive symptoms (BDI≤9), 29.5% had mild symptoms (BDI 10–15), 16.5% had moderate symptoms (BDI 16–23), and 7.2% had severe depressive symptoms (BDI≥24). Multiple regression analysis revealed that SOC accounted for 35.2% of the variance in BDI scores, with FSS contributing an additional 3.6%. Mediation analysis was conducted with BDI as the outcome variable, FSS as the mediator, and SOC as the predictor. The analysis confirmed the mediating role of family support in the SOC–BDI relationship, with the model explaining 10.3% of the variance in depressive symptoms. Based on these findings, future studies may benefit from exploring interventions that enhance perceived family support in COPD patients.

Keywords: COPD; family support; sense of coherence; depression; mediation

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is "a common, preventable condition characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities, typically caused by significant exposure to noxious particles or gases, and influenced by host factors, including abnormal lung development" [Vogelmeier et al.,2017; Vestbo et al.,, 2013]. Prolonged exposure to harmful agents induces chronic inflammation associated with structural lung changes [Barnes, 2016; MacNee,2005; Jeffery,2000]. While smoking remains the primary cause, additional factors such as air pollution, occupational exposure, and genetic predisposition also contribute [Tahery et al., 2021; Postma et al., 2015; Ryu et al.,2024; Agustí et al., 2022]. Symptoms of COPD include dyspnea, chronic cough, and sputum production, with severity ranging from asymptomatic cases to respiratory failure [Miravitlles & Ribera, 2017; Patel, 2024]. According to the World Health Organization (WHO), COPD ranked as the fourth leading cause of death worldwide in 2021, accounting for 3.5 million deaths, or 5% of all global mortality that year [Global Initiative for Chronic Obstructive Lung Disease, 2024; WHO, 2024].

The existing literature has consistently reported high rates of psychological symptoms, including anxiety and depression, among patients with COPD [Rahi et al, 2023; Tselebis et al., 2016;

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Tselebis et al, 2014; Tselebis et al, 2011a; Yohannes & Alexopoulos, 2014]. However, few studies have investigated protective psychological factors that may support patient adaptation to COPD [Tselebis, et al., 2013; Keil, 2017]. Two key positive psychological constructs examined in this context are the sense of coherence and perceived family support [Tselebis et al., 2013, Keil et al., 2017].

According to Aaron Antonovsky, the sense of coherence refers to the individual's ability to perceive life as comprehensible, manageable, and meaningful [Antonovsky, 1979; Antonovsky, 1987], and is considered a relatively stable personal trait [Eriksson & Mittelmark, 2016]. High levels of sense of coherence have been associated with better diabetes management [Ahola et al., 2010; Odajima, & Sumi, 2018; Merakou et al., 2013] and improved quality of life in patients with chronic diseases [Delgado, 207; Kristofferzon et al., 2018; Fok et al., 2005].

The second protective factor examined in this study is perceived family support among COPD patients. Evidence from other chronic diseases, such as diabetes, indicates that higher perceived family support is linked to better glycemic control [Ilias et al., 2004; Ilias et al., AlHaidar et l., 2020; Kim et al., 2007]. Supportive family relationships also appear to contribute positively to outcomes in patients with stroke [Palmer & Glass, 2003; Evans et al., 1987], chronic kidney disease [Daneker et al., 2001; Khaira et al., 2012], and heart failure [Fry et al., 2016; Dunbar et al., 2008]. Similar associations have been observed in patients with bronchial asthma [Wood et al., 2008; Pérez-Marín et al., 2024] and cancer [Arora et al., 2007; Charos et al., 2025]. However, few studies have examined the role of family support specifically in patients with COPD [Tselebis et al., 2013].

Depression is prevalent among individuals with COPD, with rates ranging from 10% to over 50% [Pumar, 2014; Maurer, 2008], significantly higher than its prevalence of 6–8% in the general population. Patients with COPD have a 1.69-fold increased risk of developing depression [Atlantis et al., 2013]. Studies from Greece report similarly high rates of depressive symptoms in COPD patients, exceeding 42% [Tselebis et al.,2013; Tselebis A et al., 2010]. When compared to other respiratory conditions such as tuberculosis or asthma, individuals with COPD exhibit higher levels of depression [Moussas et al., 2008]. Moreover, depression is more prevalent in COPD than in other chronic diseases [Solano et al., 2006].

A substantial body of research supports a negative association between sense of coherence and depression. This relationship has been demonstrated in adolescents [Moksnes et al., 2012], healthcare professionals [Pachi et al., 2022], and patients with chronic conditions such as chronic pain, heart failure [Aguilar-Latorre et al., 2023; Nahlén & Saboonchi, 2010], and stroke [Guo et al., 2018]. Studies have also confirmed this association in individuals with major depressive disorder [Skärsäter et al., 2009; Skärsäter et al., 2005; Kouvonen et al., 2010; Carstens & Spangenberg, 1997].

During the COVID-19 pandemic, the importance of family support increased due to lockdown-related restrictions [Gostin et al., 2020; Tselebis & Pachi, 2021; Adolph et al., 2021], which reduced access to other forms of social support [Zeng at al., 2022; Sikaras et al., 2023]. Recent studies suggest that enhanced family support served as a protective factor against depressive symptoms during the pandemic [Koutsimani & Montgomery, 2023]. Moreover, recent findings indicate that family support may be the most significant component of social support in mitigating the link between depression and suicidal ideation [Blessing et al., 2023]. Previous research in COPD patients has suggested an inverse relationship between family support and depression [Tselebis et al, 2013], but the mediating role of family support has not been thoroughly explored.

Thus, the primary objective of this study was to examine the protective roles of sense of coherence and family support in depressive symptomatology among COPD patients. The central hypothesis was that enhanced family support could strengthen the protective effect of sense of coherence against depression.

Based on this framework, the following hypotheses were formulated:

H1: The sense of coherence is negatively associated with and predicts depression.

H2: Family support is negatively associated with and predicts depression.

H3: Family support mediates the relationship between sense of coherence and depression.

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2. Subjects and Methods

2.1. Study Participants

From the outpatient registry of our hospital, which is the largest pulmonary disease center in the country, a total of 200 Greek patients with a confirmed diagnosis of COPD under the age of 80 were randomly selected. Patients were excluded if they had comorbid physical illnesses (e.g., cardiovascular disease), had been hospitalized for an exacerbation of COPD within the previous six months, or had a history of major psychiatric disorders. Based on these criteria, 29 patients were excluded. An additional 28 declined to participate, resulting in a final sample of 143 participants. Participation in the study was entirely voluntary. Researchers explained the aims of the study to each participant and assured them that all information would remain confidential. Written and verbal informed consent was obtained from all participants prior to data collection. Each participant completed a semi-structured form designed by the research team to collect demographic information and completed a series of self-report questionnaires assessing depression, perceived family support, and sense of coherence. All responses were collected anonymously.

2.2. Sample Size Power Calculation

A post hoc power analysis was conducted to assess the adequacy of the sample size for linear multiple regression. The analysis was performed using G*Power software [Kang, 2021; Faul et al., 2009]. A sample size of 143 with an effect size of $f^2 = 0.15$, alpha = 0.05, and seven predictors yielded a statistical power of 0.933, which was deemed satisfactory. Furthermore, following the empirical rule proposed by Kline [Kline, 1998], a suitable sample size should be at least 10 times greater than the number of parameters examined (seven parameters were included in this study).

2.3. Ethical Considerations

This study was conducted in accordance with the ethical principles outlined in the General Data Protection Regulation of the European Union (GDPR-2016/679), the Declaration of Helsinki (1975, revised 2008), and the guidelines of the International Committee of Medical Journal Editors. The study protocol was approved by the Clinical Research Ethics Committee of the 'Sotiria" General Hospital for Chest Diseases of Athens (Approval Number: 24252/27-09-21).

2.4. Measurement Instruments

Demographic and clinical data were collected from patient medical records, including sex, age, disease duration, and the most recent spirometric value for predicted FEV_1% (Forced Expiratory Volume in 1 second).

i. Beck Depression Inventory (BDI)

Depressive symptomatology was assessed using the Beck Depression Inventory (BDI) [Beck et al., 1961]. This questionnaire captures the behavioral, emotional, and somatic symptoms experienced during the previous week. It consists of 21 items, each scored from 0 to 3 [Donias & Demertzis, 1983], with a total score ranging from 0 to 63. Scores ≥24 indicate severe depressive symptoms, scores ≤9 indicate the absence of depression, scores between 10–15 suggest mild symptoms, and scores between 16–23 indicate moderate symptoms [Donias& Demertzis, 1983]. The Greek version of the BDI has been validated and used in numerous clinical studies involving Greek populations [Tselebis et al.,2013; Sikaras et al., 2023]. The instrument has high internal consistency (Cronbach's alpha = 0.83) and test-retest reliability ranging from 0.48–0.86 in clinical populations and 0.60–0.90 in non-clinical populations [Sikaras et al., 2023].

ii. Sense of Coherence (SOC)

Sense of coherence was assessed using the 13-item version of the Sense of Coherence scale (SOC-13), developed by Aaron Antonovsky. Each item is rated on a 0 to 7 scale, yielding a total score ranging from 13 to 91, with higher scores indicating a stronger sense of coherence [Antonovsky, 1993,

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Eriksson & Mittelmark, 2017]. The validated Greek version of the SOC-13 scale was used in this study [Anagnostopoulou & Kioseoglou, 2002; Pachi et al., 2022], and has demonstrated good reliability and validity in the Greek population, with a Cronbach's alpha of 0.83.

iii. Family Support Scale (FSS)

Perceived family support was measured using the Family Support Scale (FSS) [Tselebis, A, et al., 2011,b]. This scale assesses the perceived support a person receives from cohabiting family members. It consists of 13 items, each rated from "strongly disagree" to "strongly agree" on a 5-point Likert scale. Total scores range from 13 to 65, with higher scores reflecting stronger perceived family support [Tselebis et al.,2011b; Pachi, et al., 2023]. The FSS has been employed in several Greek studies [[Tselebis et al., 2011, b; Pachi, et al., 2023] and has demonstrated good internal consistency (Cronbach's alpha = 0.80).

2.5. Statistical Analysis

Statistical analyses were conducted using SPSS v.20 (IBM Corp., Armonk, NY, USA). For continuous variables, mean values and standard deviations were computed. The prevalence of depressive symptoms was also calculated in percentage terms. Normality of distribution for continuous variables was assessed using the Kolmogorov–Smirnov test ($p > 0.05$). Independent samples t-tests were used to identify gender differences in continuous variables, with Hedges' g used to report effect sizes. Pearson correlation coefficients were computed to explore relationships between continuous variables. Assumptions for linear regression analysis were verified: the Durbin–Watson test was used to assess independence of residuals, variance inflation factor (VIF) values were examined for multicollinearity, and linearity was evaluated through visual inspection of partial plots (PPs). Multiple regression was performed to determine whether the identified predictors were significantly associated with depressive symptomatology. Mediation analysis was conducted using the Hayes PROCESS Macro for SPSS (v4.0, model 4) [Hayes, 2013; Hayes & Rockwood, 2020; Hayes, 2015] to evaluate whether family support mediated the relationship between sense of coherence and depression. A p-value < 0.05 (two-tailed) was considered to be statistically significant.

3. Results

The final sample included 107 men and 32 women (Table 1). Women demonstrated a statistically higher mean predicted FEV_1% compared to men (52.2 ± 23.2 vs. 41.5 ± 20.2, independent t-test, $p < 0.05$). Conversely, male participants reported significantly higher family support scores (55.4 ± 11.3 vs. 51.4 ± 7.7, independent t-test, $p < 0.05$). No other significant gender differences were observed.

Table 1. *Descriptive statistics of participants.*

		Age	Years of disease	Fev1%	Beck Depression Inventory (BDI)	Family Support Scale (FSS)	Sense of Coherence (SOC)
Male	Mean	64.916	8.965	41.454*	11.112	55.418*	64.178
N=107	Std. Deviation	8.158	6.276	20.238	7.150	7.152	11.347
Female	Mean	63.656	8.059	52.177*	13.719	51.375*	65.344
N=32	Std. Deviation	7.740	9.284	23.264	8.053	7.694	12.8323
	Hedges' g			0.511		0,555	
Total	Mean	64.626	8.630	43.483	11.712	54.623	64.446
N=139	Std. Deviation	8.054	7.440	21.156	7.419	7.407	11,668
*t test p<0.05							

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Table 2 presents the correlations between the continuous variables of the study. Depressive symptomatology was negatively correlated with both family support and sense of coherence (Pearson correlation, $p < 0.01$; Table 2). A positive correlation was observed between family support and sense of coherence (Pearson correlation, $p < 0.01$; Table 2).

Table 2. *Correlations among age, Years of disease, Fev1%, BDI, FSS, and SOC.*

N=139		***Age***	***Years of disease***	***Fev1%***	***BDI***	***FSS***
Years of disease	*Pearson Correlation*	*0.102*				
	Sig. (2-tailed)	*0.499*				
Fev1%	*Pearson Correlation*	*0.033*	*-0.140*			
	Sig. (2-tailed)	*0.730*	*0.503*			
Beck Depression Inventory (BDI)	*Pearson Correlation*	*-0.016*	*-0.202*	*0.045*		
	Sig. (2-tailed)	*0.856*	*0.177*	*0.640*		
Family Support Scale (FSS)	*Pearson Correlation*	*0.144*	*0.199*	*-0.188*	*-0.362**	
	Sig. (2-tailed)	*0.114*	*0.225*	*0.064*	*0.001*	
Sense of Coherence (SOC)	*Pearson Correlation*	*0.030*	*-0.057*	*0.049*	*-0.609**	*0.307**
	Sig. (2-tailed)	*0.725*	*0.708*	*0.607*	*0.001*	*0.001*
N		139	139	139	139	122
* Pearson correlations $p < 0.01$, (r: 0.1–03 weak correlation, 0.31–0.7 moderate correlation, 0.71–1 strong correlation.)						

To perform multiple regression analysis, we first assessed the linearity between the three variables (BDI, FSS, and SOC) through visual inspection of the predicted probability plots (PPs). Homoscedasticity was evaluated by visually inspecting the scatterplot of standardized residuals versus predicted values. The Durbin–Watson test was used to assess the independence of residuals, yielding a value of 1.87, which indicated no evidence of autocorrelation. The variance inflation factor (VIF) was 1.10, a value well below the threshold of 4, supporting the absence of multicollinearity (Table 3).

Table 3. *Stepwise multiple regression*

Dependent Variable: Beck Depression Inventory (BDI)	**R Square**	**R Square Change**	**Beta**	**t**	**p**	**VIF**	**Durbin–Watson**
Sense of Coherence (SOC)	0.352	0.352	-0.532	-7.065	0.001 *	1.104	1.869
Family Support Scale (FSS)	0.388	0.036	-0.199	-2.638	0.001 *	1.104	

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Notes: only statistically significant variables are included; Beta = standardised regression coefficient; * correlations are statistically significant at the $p < 0.001$ level.

Using the stepwise method, we conducted multiple regression analysis in which depressive symptomatology (BDI) was designated as the dependent variable, while sex, sense of coherence, and family support were included as independent variables. The Sense of Coherence scale accounted for 35.2% of the variance in the Beck Depression Inventory scores, with the Family Support Scale contributing an additional 3.6% (Table 3).

To examine the hypothesis that the Family Support Scale mediates the relationship between sense of coherence and depressive symptomatology (BDI), we performed mediation analysis. In this model, BDI was set as the outcome variable, FSS as the mediator, and SOC as the predictor (Figure 1). Hayes' SPSS Process Macro Model 4 was used, employing a bootstrap analysis based on 5000 samples [Hayes, 2015; Hayes & Rockwood , 2020].

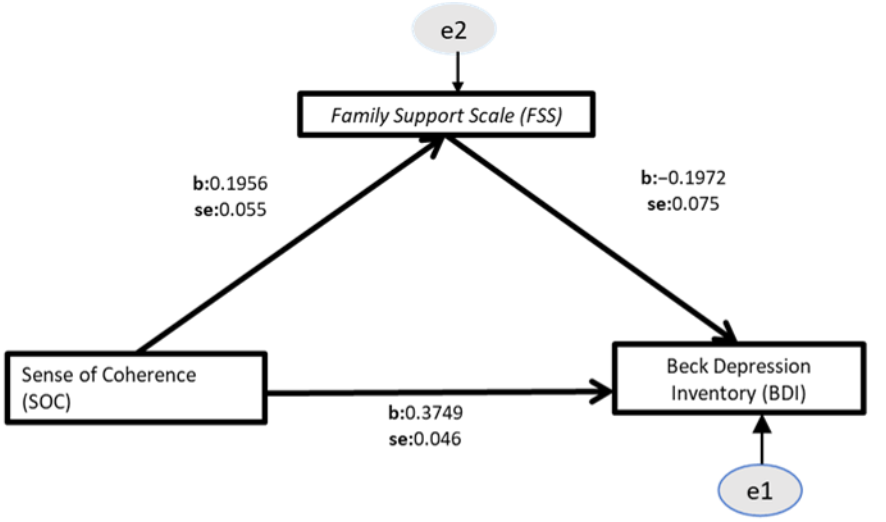

Figure 1.
Mediation analysis of Family Support Scale (FSS)on Sense of Coherence (SOC) - Beck Depression Inventory (BDI).

The analysis confirmed the mediation hypothesis, indicating that the Family Support Scale (FSS) mediates the relationship between sense of coherence (SOC) and depressive symptomatology (BDI). The indirect effect of FSS (Table 5) was statistically significant [b = -0.038, 95% CI (-0.0771, -0.0101), p ≤ 0.001]. The direct effect of SOC on BDI, in the presence of FSS as a mediator (Table 5), also remained statistically significant [b = -0.3364, 95% CI (-0.4306, -0.2421), p ≤ 0.001]. This model accounted for 10.3% of the variance in the outcome variable BDI.

Table 5. Mediation analysis of Family Support Scale (FSS) on Sense of Coherence (SOC)- Beck Depression Inventory (BDI) relationship.

Variable	b	SE	t	p	*95% ConfidenceInterval*	
					LLCI	ULCI
SOC→FSS	0. 1956	0.0553	3.5356	0.001	0. 0861	0.3052
SOC→BDI	-0.3749	0.0464	-8.0768	0.001	-0.4669	-0.2830
SOC→FSS → BDI	−0.1972	0.0748	−2.6379	0.009	−0.3453	−0.0492
Effects						
Direct	-0.3364	0.0476	-7.0646	0.001	-0.4306	-0.2421
Indirect*	-0.0386	0.0175			-0.0771	-0.0101

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Total	-0.3749	0.0464	-8.0768	0.001	-0.4669	-0.2830
*Based on 5000 bootstrapsamples						

4. Discussion

This study concurs with the findings of previous research reporting high rates of comorbid depressive symptomatology in patients with COPD [Xie et al., 2023; Zhang et al., 2011]. In the present sample, 27.7% of participants exhibited moderate to severe depressive symptoms. While the literature consistently indicates elevated rates of depression among individuals with COPD—particularly in comparison to the general population [Tselebis et al., 210; Moussas et al., 2008; Moretta et al.,2024]—the prevalence of depressive symptomatology varies significantly across studies [Moretta et al.,2024]. For instance, a Polish study reported prevalence rates of up to 50% [Homętowska et al., 2022], whereas other studies have found that 24–40% of patients with COPD experience depression [Wang et al., 2017; Maurer et al., 208; Sampaio et al., 2019]. Similarly high rates of depressive symptomatology have been documented in previous Greek studies [Tselebis et al., 2010; Moussas et al., 2008]. These discrepancies in prevalence may stem from differences in depression assessment tools, the characteristics of the study populations, and country-specific factors.

Comorbid depression in COPD patients can lead to poorer adherence to rehabilitation programs [Tselebis et al.,2014], worse clinical outcomes, more frequent exacerbations, diminished quality of life, increased mortality [Ng et al., 2007], and higher healthcare costs [Moretta et al.,2024]. Notably, the presence of depression in COPD patients is strongly associated with an elevated risk of suicidal ideation and suicidal behaviors [Roncero et al.,2022; Lin et al., 2020].

Biological theories have been proposed to explain the high prevalence of depression among individuals with COPD. Systemic inflammation and oxidative stress may represent common pathophysiological pathways linking the two conditions. Prolonged elevation of pro-inflammatory cytokines, frequently observed in COPD patients, may contribute to mood disturbances [Krishnadas et al., 2012; Young et al., 2014]. Likewise, oxidative stress, a hallmark of COPD, has been implicated in the pathogenesis of depression [Liu et al., 2015; Jiménez-Fernández et al., 2022]. Moreover, medications such as corticosteroids—particularly at high doses—have been associated with depressive disorders [Brown,209; Alturaymi et al,. 2023].

On the other hand, depression can also be viewed as a psychological response to the losses imposed by the illness, both at a practical and symbolic level [Tselebis et al., 2016]. The inability to continue occupational activities, shifts in familial and social roles, and disruptions to one's physical appearance and functioning may be perceived as significant losses [Tselebis et al., 2016, Tselebis et al., 2011a]. Some authors also argue that patients with COPD may experience profound guilt stemming from the perception of COPD as a self-inflicted illness, largely due to its strong association with smoking habits [Halding et al., 2011, Lindqvist, G., & Hallberg, 2010].

Several approaches have been studied for the treatment of depression in COPD patients, including pharmacotherapy, cognitive behavioral therapy, and pulmonary rehabilitation programs [Cafarella et al., 2012; Smith et al., 2014; Gordon et al., 2019].

Our findings support a negative association between depressive symptoms and sense of coherence (SOC), with SOC accounting for 35.2% of the variance in Beck Depression Inventory scores. This relationship has been corroborated in other chronic conditions, such as chronic pain, where SOC is considered to act as a significant determinant of depressive symptoms [Aguilar-Latorre et al.,2023; Nahlén &Saboonchi, 2010]. Our results also confirm the inverse association between family support and depression and suggest that family support mediates the relationship between SOC and depressive symptoms. In this mediating role, family support appears to further reduce depressive symptomatology among COPD patients.

Based on these findings, future research could benefit from evaluating techniques aimed at enhancing patients' sense of family support [Rosland, & Piette,2010; Gabriel et al.,2014]. Educating family members about the patient's diagnosis, prognosis, and treatment processes may strengthen

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their ability to provide appropriate and empathetic support. Including caregivers in care planning and clinical consultations, when appropriate, fosters a collaborative atmosphere and enhances the patient's perception of being cared for. Furthermore, how patients interpret family interactions may shape their perceived support; thus, interventions that help patients reframe or reinterpret ambiguous family behaviors in a more positive light may reduce feelings of isolation or neglect. Meaningful shared activities can also foster emotional closeness and enhance the sense of support. Additionally, the role of technology-based support systems should be explored, such as telemedicine platforms and digital communication tools that can overcome geographic and logistical barriers to in-person support [Barton et al., 2014; Stellefson et al., 2018]. Scheduled video calls, coordinated digital care platforms, and mobile health applications involving both patients and their family members may promote sustained interaction and perceived support [Yohannes, 2021]. In sum, improving a patient's sense of family support requires a multifaceted approach encompassing psychological, educational, relational, and technological strategies. By aligning clinical interventions with both individual cognitive factors and the broader family system, healthcare providers can foster a more supportive and resilient care environment.

Antonovsky's theory posits that SOC stabilizes around the age of 30 [Eriksson & Mittelmark 2016]; however, more recent studies suggest that SOC may be enhanced even in older adults [Feldt et al., 2011; Nilsson et al., 2010]. Interventions designed to strengthen SOC often incorporate experiential learning components, defined as the process by which knowledge is created through the transformation of lived experience. In practice, physical activity programs—such as walking, dancing, or even Zumba—have been shown to improve SOC among older populations [Thompson et al., 2021]. Similar findings have been observed in COPD patients who participated in pulmonary rehabilitation programs, which include physical exercise and demonstrated increased SOC by the end of the program [Tselebis, 2012].

The objective of this study was to examine factors that positively influence individuals with COPD, reversing the typical question of "Why does a person with a chronic illness develop depressive symptoms?" to "Why does a person with a chronic illness not develop depressive symptoms?" Accordingly, we proposed two protective factors against depression. However, a limitation of this study is that it did not examine additional potential protective factors, such as psychological resilience or spirituality. Moreover, the gender imbalance in the study sample—with male patients being overrepresented, as is common in COPD—may limit the generalizability of the findings to other diseases. It should also be noted that the design of this study precludes definitive conclusions regarding causal relationships among the variables, which should be further investigated in future research using alternative methodologies.

5. Conclusions

The high prevalence of depressive symptomatology in COPD patients has been consistently highlighted in the literature and was also supported by the present study. However, what this study contributes is the emphasis on the need for future research to focus on protective factors that support patients' mental health. The roles of sense of coherence and family support were examined and found to be inversely associated with depressive symptoms. Furthermore, family support was shown to mediate the inverse relationship between sense of coherence and depression, amplifying the protective effect of coherence and further reducing depression.

There are various techniques and interventions that promote mental health by enhancing family support and sense of coherence, thereby mitigating the depressive symptoms associated with physical illness. Evaluating the effectiveness of these interventions—both in clinical practice and future studies—would be of significant value.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author, [A.T.], upon reasonable request.

Conflicts of Interest: The authors declare no conflicts of interest.

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