



Original Research

## Comparison of mental health in individuals with primary ciliary dyskinesia, cystic fibrosis, and parent caregivers

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## ABSTRACT

**Introduction:** Individuals with chronic respiratory diseases and caregivers are at higher risk for depression and anxiety. Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) are both rare genetic diseases, characterized by recurrent respiratory infections. This study compared depression and anxiety in people with PCD (pwPCD) and CF (pwCF), and caregivers, using the screening tools recommended in the CF guidelines.

**Methods:** Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7) were administered to a PCD and CF sample. Given that PCD is extremely rare, they were matched on age and sex to pwCF at a 1:2 ratio. Similar procedures were performed with parents.

**Results:** A total of 63 patients and 129 caregivers participated: 21 pwPCD and 42 pwCF (ages 12–34 years) plus 43 caregivers of pwPCD and 86 caregivers of pwCF. A high percentage of patients scored above the cut-off for depression (PCD: 33%; CF: 43%) and anxiety (PCD and CF both: 43%), mostly mild. Similarly, a high percentage of caregivers scored above the cut-off for depression (PCD: 42–54%; CF: 45–46%) and anxiety (PCD: 47–54%; CF: 39–56%). Suicidal ideation was endorsed by 9.5% of pwPCD, 20% of mothers and 10% of fathers and 5% of pwCF, 3% of mothers, but no fathers.

**Conclusion:** A large percentage of patients and caregivers reported elevated psychological distress and suicidal ideation. Addressing psychological symptoms is critical given they are associated with poor adherence, missed clinic visits, increased inflammation and worse quality of life. Mental health screening and treatment should be integrated into PCD care.

### 1. Introduction

Primary ciliary dyskinesia (PCD) and cystic fibrosis (CF) are both rare, autosomal recessive diseases, characterized by recurrent upper and lower respiratory tract infections [1,2]. Both conditions are genetic disorders that result in multiorgan disease and male infertility, however, PCD commonly includes chronic oto-sino-pulmonary disease and hearing loss, with organ laterality defects in approximately 50% of cases [2,3]. In PCD, mutation in the cilia affect mucociliary clearance and in CF, clearance of mucus is impaired by its viscous nature, making it difficult to clear. Most prescribed treatments for people with PCD (pwPCD) are extrapolated from treatment guidelines in CF and non-CF bronchiectasis because there have been very few randomized, controlled trials (RCT)

supporting the efficacy of treatments for PCD [4–6]. Currently, most treatments for this condition are symptomatic and palliative; only azithromycin has demonstrated efficacy in a large, well-controlled RCT [7]. CF is a chronic disease caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (CFTR) and is the most common autosomal recessive, severe genetic disease among Caucasians [2]. CF causes recurrent lung infections and progressively leads to respiratory insufficiency. It affects the pancreas, digestive system, liver, and fertility. Managing CF is complex and highly burdensome [8], however, new modulator therapies for CF have been shown to be highly effective in treating the underlying cause of the disease [9].

Several studies indicate that children and adults with chronic respiratory diseases are at higher risk for depression, anxiety and elevated

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behavior problems than the general population [10–17]. A large body of evidence indicates that people with CF (pwCF) and parent caregivers have 2–3 times the prevalence of depression and anxiety than the general population [11], however less is known about these prevalence rates among pwPCD. In CF, psychological symptoms have been associated with worse adherence, worse clinic attendance, and worse clinical outcomes, including Forced Expiratory Volume in One Second (FEV<sub>1</sub>), Body Mass Index (BMI), and decrements in health-related quality of life (HRQoL) [18]. In adults with CF, a single positive screen for depression was predictive of a doubling of mortality over five years [19]. Mental health symptoms and worse HRQoL have also reported in some study on pwPCD and caregivers [20–26].

Individuals affected by PCD and CF both require a highly burdensome treatment regimen that takes 2–3 h per day, including inhaled and oral medications, antibiotics, airway clearance; in addition, pwCF must follow a high calorie diet and most take pancreatic enzymes [2,4]. Numerous studies in CF have also documented the negative consequences of depression and anxiety on adherence to these treatments, attendance at clinic and general management of the disease [27]. Several studies have documented the psychosocial challenges of people with PCD, including social stigma, isolation, embarrassment about coughing and sputum production, and increased stress [28]. In addition, both parents and patients perceive the PCD treatment regimen as highly burdensome, and report elevated symptoms of depression and anxiety [29]. Studies have also documented worse HRQoL in PCD across several domains including social and emotional functioning, vitality, role functioning and treatment burden [30]. Thus, in both populations, HRQoL is substantially impaired [23,29,31].

To date, few studies have investigated the impact of PCD on physical, social and emotional outcomes [26,32,33]. A recent study in the Netherlands showed that a considerable percentage of adolescents with PCD scored above the clinical cut-off for depression and anxiety (59% and 71%, respectively), however, a small proportion (6%) scored in the moderate to severe range [20]. Moreover, a large percentage of parents who were screened reported scores above the clinical cut-off for depression (mothers = 50%; fathers = 32%) and anxiety (mothers = 51%; fathers = 23%), with a substantial number of mothers vs. fathers reporting symptoms in the moderate to severe range (30% vs. 9%). Thus, this study aimed to assess and compare symptoms of depression and anxiety in pwPCD and CF, as well as caregivers.

In CF, The International Depression/Anxiety Epidemiological Study (TIDES) found high rates of depression and anxiety in over 6000 patients and 4000 parents across 9 countries in Europe and United States [11]. Results from the TIDES study led to development of the International Mental Health Guidelines for CF, sponsored by the Cystic Fibrosis Foundation and the European Cystic Fibrosis Society [34]. These guidelines provide recommendations for prevention, annual screening, clinical assessment and psychological/pharmacological interventions beginning at age 12 years through adulthood and for parents of children with CF from infancy through adolescence. Two well-validated screeners were recommended and are being used worldwide: the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder (GAD-7). Recent studies using these screeners have supported elevated rates of depression and anxiety in pwCF [10,35]. Unfortunately, to date, very few studies have examined psychological distress in the PCD population. Thus, the main objective of this study was to compare symptoms of depression and anxiety in pwPCD to pwCF, as well as parent caregivers, using the screening tools recommended in the CF guidelines.

## 2. Methods

### 2.1. Procedure

This study was approved by the Ethics Committee of Bambino Gesù Children's Hospital. Consecutive patients, aged ≥12 years old, with confirmed diagnoses of PCD (genetically and/or by electron

microscopy), and an independent sample of parents whose children had PCD were enrolled. In addition, a comparison group of pwCF and parent caregivers was also recruited. All patients and parents who met the age criteria agreed to participate (100%). Individuals with other significant comorbidities (e.g., autism, intellectual disabilities), and those who had been transplanted or were on the waiting list were excluded. We also excluded any parents of children who had been diagnosed within the past two years. All patients were evaluated by a psychologist and pulmonologists. As recommended in the guidelines for CF, the PHQ-9 and GAD-7 were utilized [34]. Parents of children with PCD and CF, ages birth to 17 years of age were included in the study; these parents were not paired with the patients.

All participants completed the screening tools via self-report, which took approximately 8–10 min. A psychologist immediately scored and interpreted the results to identify anyone with clinically elevated symptomatology. Supportive interventions, including psychoeducation, psychotherapy, pharmacological treatment and referrals were provided, if necessary. No respondents were currently on any antidepressant medications. Given that PCD is an extremely rare condition, pwPCD were matched on age and sex to pwCF at a 1:2 ratio (e.g., 1 pwPCD to 2pwCF); we performed similar matching with parents, using the age and sex of the child and sex of the parent to match at a 1:2 ratio.

*Analytic Plan.* Statistical analysis was performed using SPSS statistical software (IBM SPSS Statistics 20; Chicago, IL, USA). Analyses were calculated for continuous variables, frequencies (%), with quantitative variables summarized as means and standard deviations (SDs). T-tests were used in the between-group comparisons. Relationships among psychological symptoms and clinical outcomes were evaluated with Pearson's correlation coefficient.

### 2.2. Measures

#### 2.2.1. Demographic characteristics and clinical data

All participants completed a basic demographic form prior to screening (e.g., age, gender). Clinical parameters were obtained from chart review for all patients: (a) FEV<sub>1</sub>% predicted, (b) Body Mass Index (BMI), and (c) number of pulmonary exacerbations (PEX) in the previous 12 months. PEX were defined by the presence of three or more of the following seven items: 1) increased cough, 2) change in sputum volume and/or color, 3) increased shortness of breath perceived by the patient or parent, 4) decision to start or change antibiotic treatment because of perceived pulmonary symptoms, 5) malaise, tiredness, fatigue or lethargy, 6) new or increased hemoptysis, and 7) temperature >38 °C malaise, tiredness, fatigue or lethargy, 6) new or increased hemoptysis, and 7) temperature >38 °C [36].

#### 2.2.2. PHQ-9 (Patient Health Questionnaire)

The PHQ-9 [37] is a brief, self-administered and easily scored measure of depressive symptoms with 9 items that map onto diagnostic criteria for Major Depressive Disorder (MDD; DSM-5) [38]. It has extensive evidence of internal consistency (Cronbach's alpha = 0.86–0.89), sensitivity and specificity. Each symptom/item is rated according to its frequency, using a 4-point rating scale ranging from 0 (*not at all*) to 3 (*nearly every day*) over the past two weeks. It includes a question about suicidal ideation (# 9) which asks: "thoughts that you would be better off dead, or of hurting yourself," over the last 14 days. Severity of depressive symptomatology is categorized as "no symptoms" (0–4), "mild" (5–9), "moderate" (10–14) and "severe" (>15). The validated Italian version was used in all cases. PHQ-9 is free and available in all major world languages (<http://www.phqscreeners.com>).

#### 2.2.3. GAD-7 (Generalized Anxiety Disorder)

The GAD-7 [39] is a self-administered measure of anxiety, consisting of 7 items measuring symptoms of generalized anxiety and has extensive reliability and validity data (Cronbach's alpha = 0.92). Each symptom/item is rated according to its frequency, using a 4-point scale ranging

from 0 (*not at all*) to 3 (*nearly every day*) over the past two weeks. GAD-7 total scores range from 0 to 21. Severity of anxiety is categorized as “no symptoms” (0–4), “mild” (5–9), “moderate” (10–14) and “severe” (>15). The validated Italian version was used in all cases. GAD-7 is free and available in all major world languages (<http://www.phqscreeners.com>).

### 3. Results

#### 3.1. Demographic characteristics and clinical data

Descriptive demographic and clinical data are presented in Table 1. A total of 63 patients and 129 caregivers were enrolled: 21 pwPCD, ranging in age from 12 to 28 years, and 42 pwCF, ranging in age from 12 to 34 years. Mean age of the children of the parents who participated was 11.0 years ( $SD = 3.5$  years, range 6–17 years). There were 43 caregivers in the PCD group (24 mothers, 19 fathers) and 86 caregivers in the CF group (48 mothers, 38 fathers). Mean age of the children with PCD whose parents participated in the study was 12.5 years ( $SD = 3.4$  years, range 6–17 years). In terms of medical characteristics, mean  $FEV_1$ pred in PCD and CF patients was 89% and 91%, respectively and mean number of pulmonary exacerbations (PEX) in the previous 12 months in pwPCD was 1.4 and 1.2 in pwCF. Average BMI was 21.5 in pwPCD and 19.7 in pwCF. Most of the pwCF were pancreatic insufficient (83%,  $N = 35$ ) and a small number had diabetes (14%,  $N = 6$ ). No statistically significant differences were found between the groups on age, gender or any medical parameters; thus, the matching procedures were successful.

#### 3.2. Prevalence and severity of symptoms of depression in PCD and CF

Our data revealed that a high percentage of patients with PCD and CF, as well as caregivers, reported scores in the mild range or higher. Mean scores on the PHQ-9 for pwPCD was 4.3 and 4.8 in pwCF. By using the standard clinical cut-off of  $\geq 5$  which includes mild to severe symptomatology, 33.3% of pwPCD and 42.9% of pwCF reported elevated symptoms of depression. The majority of pwPCD fell in the mild range with only one individual scoring in the moderate range and no one scoring in the severe range. Similarly, in the CF sample all participants scored in the mild range of depression (see Fig. 1 and Table A-Appendix 1).

For parents, mothers and fathers in the PCD group had a mean score of 5.5 and 5.3, respectively. In the CF group, mean scores for mothers and fathers were 5.2 and 4.6, respectively. In the PCD group, 54.2% of mothers and 42.1% of fathers scored in the elevated range of depression. Most parents endorsed mild symptoms (41.7% of mothers, 26.3% of fathers), with some endorsing symptoms in the moderate range (8.3% of mothers, 15.8% of fathers), and 4.2% of mothers and 0% of fathers scoring in the severe range. Similarly, in the CF group, elevated symptoms of depression were found in 45.8% of mothers and 44.7% of fathers. The majority of parents fell in the mild range (29.2% of mothers,

36.8% of fathers), with 14.6% and 2.6%, respectively scoring in the moderate range, and 2% of mothers and 5.2% of fathers scoring in the severe range (see Fig. 1 and Table A in Appendix 1 for means and standard deviations).

Importantly, a substantial proportion of participants endorsed suicidal ideation, which is questions #9 on the PHQ-9: 9.5% of pwPCD, 20% of mothers and 10% of fathers endorsed this item. Suicidal ideation was endorsed by 5% of pwCF and 3% of mothers, however, no fathers endorsed this item.

To compare differences in depression between PCD and CF, a *t*-test was performed to compare the means of the two independent groups. No significant differences were detected for either patients [ $t = -0.7$  (62),  $p > .05$ ] or parents [mothers:  $t = 0.3$  (71),  $p > .05$ ; fathers:  $t = 0.5$  (56),  $p > .05$ ]. Furthermore, no gender differences in depression scores were found for either patients [PCD:  $t = 0.8$  (20),  $p > .05$ ; CF:  $t = 0.8$  (41),  $p > .05$ ;] or parent caregivers [PCD:  $t = 0.2$  (42),  $p > .05$ ; CF:  $t = 0.6$  (85),  $p > .05$ ].

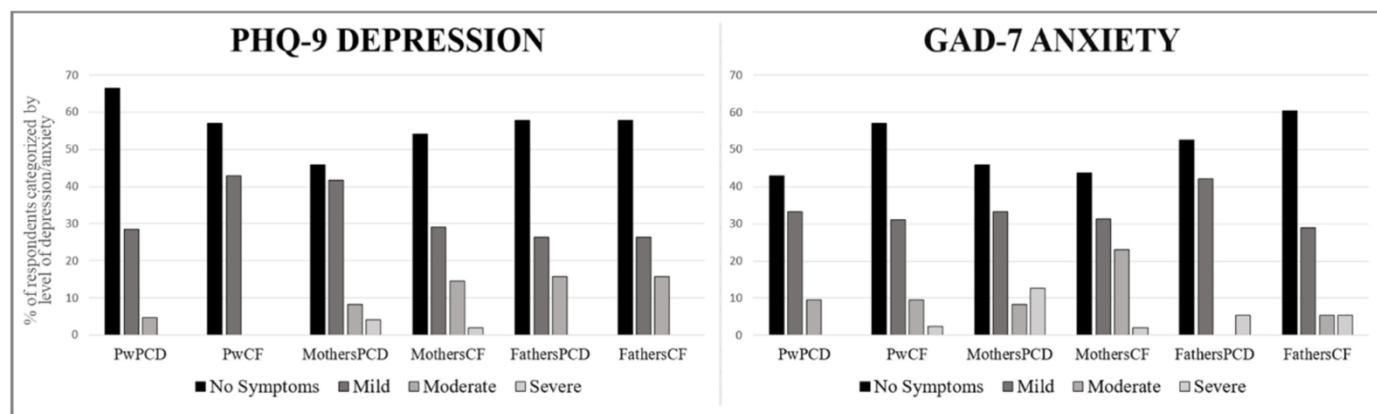
#### 3.3. Prevalence and severity of symptoms of anxiety in PCD and CF

Our results showed that a high percentage of both patients and caregivers experienced symptoms of anxiety above the clinical cut-off on the GAD-7. The mean score for pwPCD was 4.6 and in pwCF it was 4.8. Elevated symptoms of anxiety were reported by 43% of both pwPCD and CF. In terms of severity, most pwPCD fell in the mild range (33.3%), with 9.5% scoring in the moderate range, and none reporting severe symptoms. Similarly, most pwCF fell in the mild range (31.1%), with 9.5% and 2.4% scoring in the moderate range and severe range, respectively. In the PCD group, mothers and fathers mean scores ranged from 6.6 to 4.7, respectively. In the CF group, mothers and fathers mean scores ranged from 5.1 to 4.5, respectively. For parents of pwPCD, elevated symptoms of anxiety were found in 54.2% of mothers and 47.4% of fathers. Although most of these parents fell in the mild range (33.3% of mothers, 42.1% of fathers), a noticeably larger proportion of mothers than fathers fell in the moderate to severe range (21% of mothers versus 5.3% of fathers). In the CF group a large percentage of parents scored in the elevated range of anxiety, with more mothers (56.2%) than fathers (39.5%) endorsing elevated symptoms. In a pattern similar to parents in the PCD group, most scored in the mild range (31.3% of mothers, 28.9% of fathers), however, a larger percentage of mothers than fathers reported symptoms in the moderate to severe range (25% of mothers versus 11% of fathers) (see Fig. 1 and Table A in Appendix 1 for means and standard deviations). To compare differences in anxiety between PCD and CF a *t*-test was performed to compare the means of the two independent groups. No significant differences between groups were found for either patients [ $t = -0.3$  (62),  $p > .05$ ] or parents [mothers:  $t = 0.8$  (71),  $p > .05$ ; fathers:  $t = 0$  (56),  $p > .05$ ]. No gender differences in anxiety scores were found either for patients [PCD:  $t = 1.6$  (20),  $p > .05$ ; CF:  $t = 0.6$  (41),  $p > .05$ ] or parent caregivers [PCD:  $t = 1.3$  (42),  $p > .05$ ; CF:  $t = 1$  (85),  $p > .05$ ].

**Table 1**  
Participants characteristics.

	PCD			CF		
	pwPCD $N = 21$	Mothers $N = 24$	Fathers $N = 19$	pwCF $N = 42$	Mothers $N = 48$	Fathers $N = 38$
Age, mean ( $SD$ )	17.6 (6.0)	45.0 (6.7)	46.7 (8.7)	17.3 (5.5)	43.7 (5.8)	47.7 (5.6)
Male $N$ (%)	12 (57)	–	–	22 (52)	–	–
<b>Clinical parameters</b>						
$FEV_1$ , mean ( $SD$ )	88.8 (23.3)	–	–	91.2 (22.1)	–	–
BMI ( $Kg/m^2$ ), mean ( $SD$ )	21.5 (3.0)	–	–	19.7 (3.7)	–	–
PEX in 12 mths, mean ( $SD$ )	1.4 (2.2)	–	–	1.2 (1.0)	–	–
Pancreatic insufficiency $N$ (%)	–	–	–	35 (83.3)	–	–
Diabetes $N$ (%)	–	–	–	6 (14.3)	–	–

Abbreviations: pw = people with; PCD = Primary Ciliary Dyskinesia; CF= Cystic Fibrosis;  $SD$ = Standard Deviation;  $FEV_1$  = percentage of forced expiratory volume in 1 s; BMI= Body Mass Index; PEX = number of pulmonary exacerbations.



**Fig. 1.** Percentage of depression and anxiety among pwPCD, pwCF and parent caregivers  
Abbreviations: pw = people with; PCD= Primary Ciliary Dyskinesia; CF= Cystic Fibrosis; PHQ-9 = Patient Health Questionnaire-9 item; GAD-7 = Generalized Anxiety Disorder 7-item.

**3.4. Relationships among psychological symptoms and clinical outcomes in PCD and CF**

No associations were found between depressive symptoms and clinical variables either in those with PCD or CF. A moderate positive correlation was found between anxiety and lung function ( $r = 0.63, p < .01$ ). PwPCD who reported more symptoms of anxiety had higher lung function. In contrast, no significant associations were found between symptoms of anxiety and FEV<sub>1</sub>, BMI or PEx for pwCF. For parents in the PCD group, a significant negative correlation was found between depressive symptoms and number of PEx, with higher depressive symptoms associated with fewer exacerbations (see Table 2). For parents in the CF group, a significant association was found between symptoms of anxiety and FEV<sub>1</sub>; parents who reported more symptoms of anxiety had children with lower lung function (see Table 2).

**4. Discussion**

This is the first study to compare symptoms of depression and anxiety in these two rare, genetic pulmonary diseases. The diagnosis of a rare disease in a child has a major impact on the family system, including both the identified patient and his or her parents. Overall, we found similar rates of depression and anxiety in both well-matched groups, analysing data from both the patient and parent perspective. In general, a large proportion of both patients and parents reported elevated symptoms of depression and anxiety, although most of their scores fell

into the mild range. Identifying mild symptomatology is critically important for prevention and for reducing the risk of worsening trajectories of depression and anxiety, and improving quality of life [8]. The results for PCD are quite similar to the only other published studies documenting mental health using these standardized screening tools [20]. Importantly, we found that both pwPCD and parent caregivers reported very high rates of suicidal ideation (ranging from 9.5% for pwPCD to 10–20% for parents). Suicidal ideation was not reported in the prior PCD study. These data suggest that mental health is a significant issue in PCD and that more attention should be paid to its assessment and treatment.

Several reasons may explain these elevated rates of psychological distress. First, it is quite challenging to get an accurate diagnosis of PCD and it often takes several years of medical consultations to identify this condition [40]. Second, there are few approved treatments for pwPCD in contrast to the remarkable advances in treating CF [9]. Both conditions share concerns about cross-infection, which can lead to greater social isolation, and both require a complex, time-consuming and highly burdensome treatment regimen. These are significant risk factors for both depression and anxiety and impaired health-related quality of life [8].

In CF there are nationally supported foundations in Europe and the US which address the medical and psychosocial challenges of living with CF, whereas in PCD, there are few structured, national organizations addressing the needs of these individuals and their families. For example, most CF Centers in Europe have a strong psychoeducational focus, and clinical psychologists are available to assess and treat symptoms of depression and anxiety, and provide evidence-based interventions. These services are often not available for patients with PCD. The high rates of suicidal ideation found in this study are of serious concern and strongly indicate that PCD centers should be developing guidelines for mental health assessment and treatment following the paradigm that is now well-established in CF [20,34].

In terms of the selection of screening tools, one prior study in PCD [32] utilized the Hospital Anxiety & Depression Scale (HADS) [41] and found no differences in symptoms of depression and anxiety between pwPCD and healthy controls. This is likely due to the lack of sensitivity of the HADS, which has been shown to consistently under-estimate psychological symptoms [11]. Furthermore, a recent large-scale study of the HADS in CF demonstrated that this scale does not factor into the 2 proposed dimensions (depression, anxiety), but rather produces 3 factors which are difficult to interpret [42]. The HADS also does not map onto the diagnostic criteria for depression or anxiety in the DSM V [38]. In contrast, the PHQ-9 and GAD-7 have been recommended by the majority of international medical guidelines groups (NICE; USPSTF) [43,44] are free and available in all major world languages, and

**Table 2**  
Associations among psychological symptoms and clinical outcomes.

	PwPCD			PwCF		
	FEV <sub>1</sub>	PEX	BMI	FEV <sub>1</sub>	PEX	BMI
PHQ-9	r = .23	r = -.11	r = -.02	r = .00	r = .10	r = -.20
GAD-7	r = .63**	r = -.13	r = -.14	r = -.03	r = .19	r = -.02
	Parents PCD			Parents CF		
	FEV <sub>1</sub>	PEX	BMI	FEV <sub>1</sub>	PEX	BMI
PHQ-9	r = .14	r = -.38*	r = .20	r = -.16	r = .20	r = .17
GAD-7	r = .25	r = -.36	r = .10	r = -.24*	r = .17	r = -.02

Notes: Data are presented as Pearson's correlation coefficients (r, two-tailed): \*p < .05, \*\*p < .01. Abbreviations: PHQ-9 = Patient Health Questionnaire-9 item; GAD-7 = Generalized Anxiety Disorder 7-item; FEV1 = percentage of forced expiratory volume in 1s; BMI =Body Mass Index; PEX = number of pulmonary exacerbations over past year.

importantly, include the assessment of suicidal ideation.

Our results also indicated that mothers of children with both PCD and CF reported higher scores than fathers, with a larger percentage endorsing moderate to severe levels of symptomology. Although there is little empirical evidence on the mechanisms underlying these parental differences, there is some evidence in CF that mothers take on more of the responsibility for daily treatments than fathers and that this is related to symptoms of depression [45]. More research on the role of caregiving in relation to mental health in these two chronic conditions is clearly needed.

In our study, symptoms of anxiety in pwPCD were modestly correlated with FEV<sub>1</sub> values and parental anxiety was also reported in relation to exacerbations and lung function. Finally, parental anxiety in the CF group was modestly associated with lower lung function, suggesting that they had worries about long-term health.

#### 4.1. Strengths and limitations

Strengths of this study include the detailed and successful matching of these two rare disease populations in terms of their demographic and medical characteristics. No differences were found between the PCD and CF group on any of these parameters. Thus, these comparisons are likely to generalize to larger samples. In addition, the mental health screening measures recommended in the international guidelines for CF were utilized in this study, providing new data on the alarming rates of suicidal ideation endorsed by both patients with PCD and parents. These rates of suicidal ideation are much higher in PCD than those reported for CF [10,46] which indicates there is an urgent need to include systematic screening of depression and anxiety in this population. It is also noted that there is very little structured psychosocial support available to pwPCD and their families and that not all centers have a multidisciplinary team available to provide adequate psychological assessments and treatment.

The major limitation of this study was its small sample size. PCD is an extremely rare disease and is also often misdiagnosed. These findings should be confirmed with a larger sample, likely requiring a multi-center study.

## 5. Conclusion

This is the first study comparing symptoms of depression and anxiety in individuals with PCD and CF. Elevated psychological distress was found in a large percentage of patients as well as parent caregivers, and risk for suicide was also endorsed by a substantial number of respondents, particularly in the PCD group. Addressing these psychological symptoms is critical given that depression, in particular, is associated with poor adherence, missed clinic visits, increased inflammation and greater morbidity [19,47–49]. Mental health screening and treatment should be integrated into the physical care of people with serious, chronic respiratory conditions.

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## CRediT authorship contribution statement

**Sonia Graziano** Conceptualization, design, analyses, writing original draft and preparation of this manuscript. **Nicola Ullmann** Assisted with the design, contributed to design and enrollment, and manuscript

write-up. Review & editing. **Raffaella Rusciano** Assisted with the design, contributed to design and enrollment, and manuscript write-up. **Annalisa Allegorico** Contributed to the data entry and the analyses. **Francesca Boldrini** Contributed to the analyses. **Lorenza Rosito** Contributed to the analysis. **Alexandra L. Quittner** Writing original draft and preparation of this manuscript. Review & editing, mentoring. **Renato Cutrera** Contributed to recruitment and write-up of the manuscript. **Paola Tabarini** Assisted with the conceptualization, design, and write-up of the manuscript.

## Declaration of competing interest

There are no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2022.107095>.

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