**Depression, anxiety and resilience during COVID-19 in Dutch patients with Cystic Fibrosis or Primary Ciliary Dyskinesia and their caregivers**

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**Declarations of interest:** none.

**ABSTRACT**

*Background.* The COVID-19 pandemic has spread across the world, leading to government measures associated with a negative impact on mental health. The aim of this study was to evaluate the impact of COVID-19 on depression, anxiety and resilience in Dutch people with cystic fibrosis (PwCF) or primary ciliary dyskinesia (PwPCD) and their caregivers during the pandemic.

*Methods.* Adolescents (12-17 years), adults and caregivers of children (0-17 years) with CF or PCD completed questionnaires on depression (PHQ-9), anxiety (GAD-7) and resilience (BRS) between September 2020 and February 2021. The psychosocial impact of COVID-19 was measured by the Exposure and Family Impact Survey (CEFIS) Part 2. Mixed model analyses compared PHQ-9 and GAD-7 results to participants’ pre-pandemic scores.

*Results.* 110 participants (10 PwCF, 31 PwPCD, 52 CF caregivers, 17 PCD caregivers) completed questionnaires during the pandemic. Pre-pandemic outcomes were available for 87 participants. The prevalence of symptoms of depression and anxiety (PHQ-9 or GAD-7 scores ≥5) in PwCF and PwPCD and their caregivers before and during the pandemic was high, with an increase in depression in PwCF (2.75; 95%-CI: 0.82 to 4.68) and increase in anxiety in CF caregivers (1.03; 0.09 to 1.96) during the pandemic. Resilience was within the normal range for all groups, CEFIS scores corresponded to a low to normal impact.

*Conclusion.* PwCF and PwPCD and their caregivers were at high risk of increased depression and anxiety symptoms both before and during the pandemic, which emphasizes the importance of mental health screening and psychological care in CF and PCD.

**INTRODUCTION**

The novel coronavirus disease (COVID-19), which predominantly affects the respiratory system, has become a global pandemic which has led to the implementation of government measures all around the world. For the Netherlands specifically, it resulted in a national lockdown and quarantining people with suspected or diagnosed COVID-19, measures which might increase social isolation and loneliness, with a negative impact on mental health (1–4). People with chronic respiratory diseases such as cystic fibrosis (CF) or primary ciliary dyskinesia (PCD) and their caregivers are already at increased risk of developing symptoms of depression and anxiety (5,6).

CF is a chronic, genetic disease caused by mutations in cystic fibrosis transmembrane conductance regulator (CFTR) genes, involving multiple organ systems, resulting in progressive lung disease and a variation of comorbidities (7). Viral respiratory tract infections are usually more prevalent and more severe in people with CF (PwCF), however, COVID-19 infections in children with CF generally follow a mild course (8,9). Due to the progressive nature and burden of disease and treatments, the prevalence of symptoms of depression and anxiety in PwCF has shown to be two to three times higher than in community samples (10), which has been associated with negative health outcomes including worse adherence, increased hospitalizations, and decreased pulmonary function and health-related quality of life (5). However, a study in PwCF did show higher levels of resilience than healthy reference groups, which might suggest they have a strong sense of “bouncing back from adversity” and more readily recover from stressful situations (11).

PCD is a rare hereditary syndrome resulting in ciliary dysfunction, which leads to neonatal respiratory distress, chronic wet cough and recurrent airway infections (12,13). Though generally assumed to have a much more favorable prognosis than CF, subgroups of PCD with CCNO, CCDC39 and CCDC40 mutations seem to have a progressive loss of lung function almost similar to CF (14).

Children with PCD and their caregivers revealed elevated symptoms of depression or anxiety, which were associated with worse health-related quality of life (HRQoL) (6,15,16).

The COVID-19 pandemic has had a negative impact on mental health of the general population, with heightened levels of stress and symptoms of depression during the first wave of the pandemic (17). A systematic review, including 10 different countries worldwide, showed that the prevalence of symptoms of depression and anxiety in children and adolescents during the COVID-19 outbreak was 34.5% and 41.7% respectively (18).

Recent publications investigating mental health in PwCF during COVID-19 show contradicting results ranging from lower (19,20), to normal (21,22), to higher levels of symptoms of anxiety (23,24), and no difference in symptoms of depression compared to healthy peers (23). Caregivers of CF reported the same opposing results in mental health during COVID-19, ranging from no change (23) to increased levels of anxiety in mothers (21). People with PCD (PwPCD) did not report a change in levels of distress, however, their caregivers did show higher stress levels (25).

A better understanding of the mental health impact of the pandemic on this population is essential in order to investigate the need for psychological interventions. Therefore, our aims are 1) to assess the impact of COVID-19 on depression and anxiety in Dutch PwCF and PwPCD and their caregivers, by comparing pre-pandemic mental health screening outcomes to pandemic screening scores, 2) to assess resilience and the COVID-19 impact score of these individuals during the pandemic, and 3) to evaluate whether the impact of COVID-19 varies in individuals with different ages, gender, pulmonary function (FEV1) and Body Mass Index (BMI).

**MATERIAL AND METHODS**

1. **Study design**

The study was a quantitative, longitudinal, questionnaire screening study conducted at a single CF- and PCD-center in the Netherlands. The medical ethics committee of the Amsterdam UMC, location VUmc, the Netherlands, approved the study (METc\_2020.459).

1. **Participants and procedure**

From September 2020 to February 2021, during the second wave of the COVID-19 pandemic, all adolescents (12-17 years) with CF and caregivers of children (0-17 years) with CF, and all adolescents and adults (≥18 years) with PCD and caregivers of children with PCD from Amsterdam University Medical Centers (Amsterdam UMC) were invited to participate in the study. This was a pre-existing cohort; most of these individuals had previously (between January 2019 and March 2020) participated in the annual mental health screening program for depression and anxiety, following the International Committee on Mental Health in Cystic Fibrosis (ICMH) guidelines (26). The assessment during COVID-19 was considered an extra mental health screening.

All participants provided written informed consent. Exclusion criteria were illiteracy and insufficient understanding of the Dutch language.

2.1 Procedure  
The mental health screening procedure was as follows:

1. All participants received either online questionnaires (see 3.2 Questionnaires) through the clinical data management platform Castor EDC (27), or paper questionnaires through a member from their CF- or PCD-multidisciplinary care team (pediatric psychologist, specialized nurse or pediatrician).
2. The pediatric psychologist immediately checked the questionnaires for suicidal ideation, and contacted individuals at increased risk within three days.
3. All other measures were scored within one week.
4. The participants had the option to be contacted by the pediatric psychologist to discuss the results of the questionnaires, and to be referred to a healthcare provider if required.
5. **Measures**

3.1 Demographic and clinical characteristics

Demographic factors, including information on gender, marital status, region of residence (rural versus urban) and level of education, were collected for all participants through questionnaires. Clinical characteristics of the patients such as age, genetic mutation (if available), body mass index (BMI) plus Z-scores and lung function were obtained from patient records. Lung function was assessed through prebronchodilator spirometry as part of standard care according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (28), and was expressed in forced expiratory volume in 1 second (FEV1) in percentage of the predicted value. Lung function tests were only performed in individuals ≥ 6 years old, and normal FEV1-values were defined as ranging between 80 and 100%.

3.2 Questionnaires

*Patient Health Questionnaire (PHQ-9, Dutch version)*

The PHQ-9 measures depressive symptoms, using a set of 9 items that consist of the nine criteria on which the minor and major depressive disorder diagnoses from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) are based (10,29). The scores per item range from 0 (not at all) to 3 (nearly every day). The following interpretive outcomes were developed to measure severity of depression symptoms: 1–4 = minimal, 5–9 = mild, 10–14 = moderate, 15–19 = moderately severe, and 20–27 = severe. For this study, a score of ≥ 5 was defined as having symptoms of depression, and a score of ≥ 10 as clinically elevated. The minimal clinically important difference (MCID) for the PHQ-9 is five points on the 0 to 27 point scale (30).

*Generalized Anxiety Disorder Scale (GAD-7, Dutch version)*The GAD-7 is a screening tool for generalized anxiety disorder, as classified by the DSM-V. It consists of 7 items, rated on a 4-point scale ranging from 0 (not at all) to 3 (nearly every day). Anxiety outcome scores range from 0 to 21: 1–4 = minimal, 5–9 = mild, 10–14 = moderate, and ≥15 = severe (10,31). For this study, a score of ≥ 5 was defined as having symptoms of anxiety, and a score of ≥ 10 as clinically elevated. The MCID for the GAD-7 is 3.8 points on the 0 to 21 point scale (32).

*Brief Resilience Scale (BRS, Dutch version)*  
The BRS is a tool to assess one’s resilience, the ability to bounce back and recover from stress. It consists of 6 items, of which three are rated on a 5-point scale ranging from 1 (strongly disagree) to 5 (strongly agree), and the other three are rated on a reverse 5-point scale ranging from 5 (strongly disagree) to 1 (strongly agree). Outcome scoring is as follows: 1 - 2.99 (low resilience), 3 – 4.30 (normal resilience) and 4.31 – 5 (high resilience) (33).

*COVID-19 questionnaire*

Five self-developed items about COVID-19 were added, which were formulated by a team of pediatricians and pediatric psychologists. These items are: (i) I suspect to have been infected by COVID-19 (yes or no), (ii) I have tested positive for COVID-19 (yes or no), (iii) my symptoms of anxiety have increased since COVID-19 (rated on a 5 point scale from 1 (strongly disagree) to 5 (strongly agree)), (iv) my symptoms of depression have increased since COVID-19 (strongly disagree to strongly agree), and (v) how would you describe your mental health now, compared to prior to the pandemic (rated on a 3 point scale: deteriorated (1) – no change (2) – improved (3)).

*COVID-19 Exposure and Family Impact Survey (CEFIS, Dutch version, see Appendix)*

The CEFIS consists of two parts: part 1 evaluates exposure to potential traumatic experiences related to the pandemic, and part 2 assesses the impact of the COVID-19 pandemic on one’s family (34). The CEFIS was developed and validated by the Center for Pediatric Traumatic Stress (35). For this study, part 2 of the CEFIS was used, consisting of 12 items that assess the impact of COVID-19. Out of these 12 items, 10 used score options on a four-point Likert scale ranging from 1 (made it a lot worse)to 4 (made it a lot better)*,* and 2 items used a 10-point distress scale (no distress to extreme distress). Higher scores indicate a more negative impact and/or higher distress. The Impact Score for the CEFIS ranges from 12 to 60, for the CEFIS-AYA it ranges from 12 to 70. The CEFIS was translated according to FDA (2009) and EMA guidelines (2007). Two native Dutch speakers independently translated part 2 of the CEFIS from English to Dutch. They resolved discrepancies and reached consensus by teleconference. The consensus measure was back-translated to English by two Dutch speakers with strong English skills, and followed by assessment of four individuals who approved its comprehensiveness in Dutch.

For adolescents and young adults (12 to 30 years) specifically, the Family Exposure and Impact Survey for Adolescents and Young Adults (CEFIS-AYA) was developed (36), translated to Dutch following the FDA and EMA guidelines. The Impact Score for the CEFIS-AYA ranges from 12 to 70.

1. **Statistical analysis**

The sample size was calculated (using software G\*power) based on the primary aim of this study, meaning, to detect the difference in depression and anxiety symptoms according to the GAD scores in between pre and post pandemic. Considering a minimal clinically important difference (MCID) of 3.8 of the GAD-7 as a reference, providing an effect size of 0.53 (32), type-I error rate of 0.05 and a power of 0.90, a required sample size of 41 participants was calculated.

All further analyses were performed in IBM Statistical Packages for the Social Sciences (SPSS) version 27.0. Descriptive analyses were used to summarize the demographic and clinical characteristics of the participants and outcome scores of the PHQ-9, GAD-7, BRS and CEFIS. Mixed model analysis was used to compare the difference in PHQ-9 and GAD-7 scores at two time-points from the same study population, and to identify possible effect modifiers. Demographic characteristics such as age (continuous), gender (dichotomous) and the clinical characteristics BMI (continuous) and FEV1 (dichotomous; <80% = low, ≥80% = normal) were added to the mixed model regression analysis to assess their effect on the difference in PHQ-9 and GAD-7 scores before and during the pandemic. These analyses were performed separately for PwCF or PwPCD and caregivers. Age, BMI and FEV1 were collected for PwCF and PwPCD, and for caregivers it concerned their child’s age, BMI and FEV1. Logistic Generalized estimating equations (GEE analyses) were performed to compare symptoms of depression and anxiety between CF and PCD groups. Results were considered significant when the p-value was ≤0.05.

**RESULTS**

1. **Participants, demographics and clinical characteristics**

In total, 209 individuals were invited to participate in the study, of which 110 (53%) responded: 10 adolescents with CF (9%), 52 caregivers of children with CF (47%), 9 adolescents with PCD (8%), 22 adults with PCD (20%) and 17 caregivers of children with PCD (16%). Of the caregivers of children with CF, 38 were caregivers of children <12 years old, and 14 of adolescents. For PCD caregivers, 9 caregivers had children <12 years old, and 8 had adolescent children.  
Out of the 110 respondents, 87 had previously participated in mental health screening and could provide pre-pandemic outcomes (6 adolescents CF (7%), 44 CF caregivers (50%), 6 adolescents with PCD (7%), 19 adults with PCD (22%), 12 PCD caregivers (14%)).

Demographics during the pandemic of all participants are presented in Table 1. Most participants were female (56%) and participants were mainly highly educated (59%). In the demographic questionnaire, 100% PwCF filled in that they are currently receiving or have received psychological support in the past year. In PwPCD, 26% are currently receiving or have received psychological support in the past year, and 13% need psychological support. Twenty-nine percent of CF caregivers and 53% of PCD caregivers are currently receiving or have received psychological support in the past year; 10% of CF caregivers emphasized the need for psychological support.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Demographic characteristics** | **Patients  with CF (n %)** *n=10* | **Patients  with PCD\* (n %)** *n=31* | **Caregivers  CF (n %)** *n=52* | **Caregivers  PCD (n %)** *n=17* |
| Gender |  |  |  |  |
| Male | 4 (40) | 14 (45) | 24 (46) | 7 (41) |
| Female | 6 (60) | 17 (55) | 54 (54) | 10 (59) |
| Region of residence |  |  |  |  |
| City | 6 (60) | 10 (32) | 23 (44) | 10 (59) |
| Village | 2 (20) | 14 (45) | 11 (21) | 4 (23) |
| Countryside | 1 (10) | 1 (3) | 3 (6) | 1 (6) |
| Unknown | 1 (10) | 6 (20) | 15 (29) | 2 (12) |
| Level of education\*\* |  |  |  |  |
| Lower education | 3 (30) | 12 (39) | 11 (21) | 3 (18) |
| Higher education  Unknown | 6 (60)  1 (10) | 19 (61) 0 (0) | 26 (50) 15 (29) | 14 (82) 0 (0) |
| Marital status |  |  |  |  |
| Single | 0 (0) | 6 (20) | 1 (2) | 1 (6) |
| Married/living together | 0 (0) | 14 (45) | 32 (61) | 14 (82) |
| Divorced | 0 (0) | 0 (0) | 3 (6) | 2 (12) |
| Widowed | 0 (0) | 1 (3) | 1 (2) | 0 (0) |
| Not applicableᶲ | 10 (100) | 9 (29) | 0 (0) | 0 (0) |
| Unknown | 0 (0) | 1 (3) | 15 (29) | 0 (0) |
| Psychological care |  |  |  |  |
| Received psychological support in the past year | 5 (50) | 5 (16) | 9 (17) | 5 (29) |
| Currently receiving psychological support | 5 (50) | 3 (10) | 6 (12) | 4 (24) |
| Need for psychological support | 0 (0) | 4 (13) | 5 (10) | 0 (0) |

**Table 1. Demographic characteristics of the participants, n = 110**\* 9 adolescents, 22 adults  
\*\* Lower education = Primary school, basic vocational education, general and vocational secondary education. Higher education = Senior general secondary education, university of Applied Sciences, higher academic education

ᶲQuestion not asked to adolescents

Clinical characteristics for patients who completed questionnaires themselves are presented in Table 2a. Clinical characteristics for patients of whom caregivers completed questionnaires are presented in Table 2b. Mean BMI was within normal range for all patients. FEV1 was below average (<80%) for children and adults with PCD.  
 **Table 2a. Clinical characteristics of patients**

|  |  |  |  |
| --- | --- | --- | --- |
| **Clinical characteristics** | **Adolescents with CF**  N = 10 | **Adolescents with PCD**  N = 9 | **Adults with PCD**  N = 22 |
| Mean age in years (SD\*) | 15 (±2.0) | 15 (±1.6) | 40 (±18.3) |
| Genetic mutation (n %) |  |  |  |
| F508del/F508del | 6 (60) | n.a. | n.a. |
| F508del/other | 3 (30) | n.a. | n.a. |
| DNAH5/DNAH5 | n.a. | 2 (22) | 0 (0) |
| DNAI1/other | n.a. | 2 (22) | 1 (5) |
| Other | 1 (10) | 2\*\* (22) | 1\*\* (5) |
| Unknown | 0 (0) | 3 (33) | 20 (90) |
| Mean BMI× (SD)  Median Z-scores (25-75 percentile) | 19.0 (1.3)  -0.19 (-0.90 - 0.27) | 21.9 (4.9)  0.33 (-1.73 - 1.97) | 23.5 (4.0)  n.a. |
| Mean FEV1ᶲ in % of predicted (SD) | 80.4 (27.0) | 78.7 (18.5) | 73.9 (21.1) |

**Table 2b. Clinical characteristics of patients whose caregivers participated**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Clinical characteristics** | **Children with CF**  N = 21 | **Adolescents with CF**  N = 9 | **Children with PCD**  N = 6 | **Adolescents with PCD**  N = 6 |
| Mean age in years (SD\*) | 5 (±2.8) | 15 (±1.7) | 5 (±3.4) | 16 (±1.9) |
| Genetic mutation (n %) |  |  |  |  |
| F508del/F508del | 16 (76) | 6 (67) | n.a. | n.a. |
| F508del/other | 3 (14) | 3 (33) | n.a. | n.a. |
| DNAH5/DNAH5 | n.a. | n.a. | 2 (33.3) | 0 (0) |
| DNAI1/other | n.a. | n.a. | 2 (33.3) | 2 (33) |
| Other | 2 (10) | 0 (0) | 1\*\* (16.7) | 1\*\* (17) |
| Unknown | 0 (0) | 0 (0) | 1 (16.7) | 3 (50) |
| Mean BMI× (SD)  Median Z-scores (25-75 percentile) | 15.9 (1.4)  0.25 (-0.50 - 0.69) | 19.0 (2.0)  -0.26 (-1.12 - 0.63) | 15.7 (1.6)  -0.45 (-1.09 - 0.34) | 20.6 (5.4)  -0.11 (-1.73 - 1.97) |
| Mean FEV1ᶲ in % of predicted (SD) | 98.1 (17.0) | 79.9 (28.7) | 78.0 (17.0) | 79.3 (18.0) |

\* Standard Deviation

× Body Mass Index (in kg/m2)  
ᶲ Forced Expiratory Volume in 1 second.

\*\* CCDC39 or CCDC40 mutation

1. **Questionnaire outcomes**

*2.1 Depression, anxiety, resilience, CEFIS and COVID-19 related questions during the pandemic*Table 3 shows outcome scores from during the pandemic. Six participants (5.5%) showed clinically elevated (PHQ ≥ 10) scores for depression, and 12 (10.9%) for anxiety (GAD-7 ≥ 10). Seven participants (6.4%); 3 adolescents with CF, 1 adolescent with PCD and 2 adults with PCD, screened positive on suicidal ideation. Mean resilience score was within the normal range for all groups. Mean CEFIS impact scores for all patients and caregivers corresponded to a low to normal impact.

**Table 3. Outcome scores during the pandemic**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Patients with CF**  *N = 10* | **Patients with PCD** *N=31* | **Caregivers CF** *N=52* | **Caregivers PCD** *N=17* |
|  |  |  |  |  |
| Median PHQ-9 (25-75 percentile) | 5.5 (4.0 – 8.3) | 4.0 (2.0 – 8.0) | 2.0 (1.0 – 5.0) | 4.0 (1.0 – 6.0) |
| Median GAD-7 (25-75 percentile) | 3.5 (2.5 – 5.5) | 3.0 (1.0 – 8.0) | 3.0 (1.0 – 5.0) | 3.0 (1.0 – 7.0) |
| Mean resilience score (SD) | 3.35 (±0.71) | 3.26 (±0.61) | 3.48 (±0.73) | 3.50 (±0.92) |
|  | *N=9* | *N=26* | *N=37* | *N=16* |
| Mean CEFIS score (SD) | 20.1 (±10.5) | 26.5 (±9.5) | 23.3 (±10.3) | 17.6 (±8.2) |
| Mean distress score\* (SD) | 4.6 (±1.7) | 5.5 (±2.0) | 5.2 (±2.1) | 3.8 (±1.7) |
| Self-reported mental health (n %)  “Deteriorated”  “No change”  “Improved” | 1 (11)  7 (78)  1 (11) | 7 (27)  18 (69)  1 (4) | 8 (22)  24 (65)  5 (13) | 1 (6)  13 (81)  2 (13) |
| COVID-19 infection (n %)  Suspected | 2 (22) | 3 (12) | 5 (13) | 3 (19) |
| Confirmed (PCR-positive) | 0 (0) | 0 (0) | 1 (3) | 2 (12) |

\* On a scale of 1 to 10.

PHQ-9 = Personalized Health Questionnaire-9, GAD-7 = Generalized Anxiety Disorder, BRS = Brief Resilience Scale, CEFIS = COVID-19 Exposure and Family Impact Survey

**Table 4. Classification of depression and anxiety scores**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Patients with CF** | | **Patients with PCD** | | **Caregivers CF** | | **Caregivers PCD** | |
| *Pre-pandemic*  N = 6 | *Pandemic*  N = 10 | *Pre-pandemic*  N = 25 | *Pandemic*  N = 31 | *Pre-pandemic*  N = 44 | *Pandemic*  N = 52 | *Pre-pandemic*  N = 12 | *Pandemic*  N = 17 |
| **Depression (PHQ-9), n (%)** |  |  |  |  |  |  |  |  |
| Normal range  (score ≤ 4) | 5 (83) | 3 (30) | 10 (40) | 16 (52) | 34 (77) | 38 (73) | 6 (50) | 10 (59) |
| Mild range  (score 5 – 9) | 1 (17) | 7 (70) | 12 (48) | 13 (42) | 7 (16) | 12 (23) | 3 (25) | 5 (29) |
| Moderate range  (score 11 – 14) | 0 (0) | 0 (0) | 3 (12) | 2 (6) | 2 (5) | 2 (4) | 2 (17) | 2 (12) |
| Severe range (score ≥ 15) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 1 (8) | 0 (0) |
| **Anxiety (GAD-7), n (%)** |  |  |  |  |  |  |  |  |
| Normal range  (score ≥ 4) | 5 (83) | 6 (60) | 11 (44) | 20 (65) | 32 (75) | 33 (63) | 7 (59) | 12 (71) |
| Mild range  (score 5 – 9) | 1 (17) | 4 (40) | 12 (48) | 6 (19) | 9 (21) | 15 (29) | 1 (38) | 2 (12) |
| Moderate range  (score 11 – 14) | 0 (0) | 0 (0) | 2 (8) | 5 (16) | 1 (2) | 3 (6) | 3 (25) | 3 (17) |
| Severe range (score ≥ 15) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) | 1 (2) | 1 (8) | 0 (0) |

PHQ-9 = Personalized Health Questionnaire-9, GAD-7 = Generalized Anxiety Disorder

*Note: only the prevalence of participants of whom pre-pandemic scores were available are presented (n=87)*

*Hier*

*2.2 Pre-pandemic vs. pandemic scores*

Table 4 and figure 1 illustrate the prevalence and a classification of depression and anxiety scores before and during the pandemic. Results from mixed model regression analysis of the PHQ-9 scores comparing participants’ pre-pandemic outcomes to during the pandemic are portrayed in table 5. In PwCF, a significant difference in depression scores was found (difference: 2.75; 95%-CI: 0.82 to 4.68; p=0.01). In CF caregivers, a significant difference in anxiety was found (difference: 1.03; 95%-CI: 0.09 to 1.96; p=0.03) indicating an increase in scores during the pandemic. All other regression coefficients were not statistically significant.  
Logistic GEE analyses showed differences in the prevalence of symptoms of depression and anxiety between PwCF and PwPCD, with higher scores in the PCD population (depression: difference 0.15, 95%-CI: -1.10 to 1.13; anxiety: difference 0.316, 95%-CI: -0.91 to 1.55), but these were not statistically significant due to small sample sizes. Similar results were found between caregivers of both groups (depression: difference 0.83, 95%-CI: -0.18 to 1.84; anxiety: difference 0.06, 95%-CI: -0.96 to 1.08).

|  |  |  |
| --- | --- | --- |
|  | **Symptoms of depression** (PHQ-9) | **Symptoms of anxiety** (GAD-7) |
| **Patients with CF** (N=10) | 2.75 (0.82 to 4.68; **p=0.01**) | 1.37 (-0.33 to 3.07; p=0.10) |
| **Patients with PCD** (N=31) | -0.64 (-2.16 to 0.89; p=0.40) | -0.49 (-2.18 to 1.21; p=0.56) |
| **Caregivers CF** (N=52) | -0.06 (-0.94 to 0.83, p=0.90) | 0.96 (0.06 to 1.87; **p=0.04**) |
| **Caregiver PCD** (N=17) | -1.70 (-4.15 to 0.75; p=0.16) | -0.60 (-2.74 to 1.54; p=0.56) |

**Table 5. Regression coefficients, 95% confidence interval and p-values regarding the difference between pre-pandemic and pandemic depression and anxiety scores**

PHQ-9 = Personalized Health Questionnaire-9, GAD-7 = Generalized Anxiety Disorder

*2.3 Participant characteristics and depression and anxiety*

For PwCF and PwPCD, gender, age, BMI and FEV1 were not significant effect modifiers for the difference in depression and anxiety before and during the pandemic (all p-values ≥ 0.16).

In caregivers of children with CF or PCD, gender was not an effect modifier, nor was their child’s age or BMI (all p-values ≥ 0.23). However, CF caregivers whose children had low FEV1-values did have a statistically significant increase in anxiety scores (regression coefficient: 0.93, 95%-CI 0.06 to 1.79; p=0.04) during the pandemic.

**DISCUSSION**

This is the first study investigating mental health in Dutch PwCF and PwPCD and their caregivers during the COVID-19 pandemic. The prevalence of symptoms of depression and anxiety in PwCF and PwPCD and their caregivers before and during the pandemic was high, with an increase in depression in PwCF and increase in anxiety in CF caregivers during the pandemic. CF caregivers of children with a low FEV1 showed a significant increase in anxiety scores during the pandemic.

In PwPCD and PCD caregivers, no significant differences were found in depression or anxiety pre-pandemic vs. pandemic.

A possible explanation for the unchanged mental health in the PCD study population is the relatively mild prognosis of COVID-19 in PCD (37,38). One reason could be that patients and their caregivers were counseled on the effects of COVID-19 by their multidisciplinary PCD-team (e.g. psychologist, social worker, pediatricians, nurses and pulmonologists) from the start of the pandemic, and once it was clear that the threat of infection was not as severe as initially expected, they were advised to follow the general national guidelines as far as their physical condition allowed them to (39). Being updated regularly by health care professionals may have induced a sense of safety and security in our population, and recent research has demonstrated that psychological support through telehealth has positive effects of reducing symptoms of stress and depression for PwCF and caregivers (40). Furthermore, as PwPCD already implement strict guidelines such as regular handwashing and social distancing to prevent the spread of infectious diseases (41), they might have felt more validated as the general population now had to follow these guidelines as well.   
 Compared to the general Dutch population, our study population showed a lower prevalence of symptoms of depression and anxiety during the COVID-19 pandemic, which was 7.1% for symptoms of depression and 16.7% for anxiety in children and adolescents (42), and 17.2% for symptoms of depression and anxiety in Dutch adults (43). Furthermore, a total of 19.5% of our population self-reported a decline in mental health during the pandemic, which shows that even if the questionnaire score indicates no difference, a participant’s own experience is an important factor to take into consideration when providing psychological care. Resilience scores in our study population was in line with the general Dutch population (44), as both scores are within the “normal” range.

A strength of this study was the study design. By using standardized, validated tests at two different time points, we provided a relatively objective and reliable insight into the development of mental health during a global pandemic. Another strength was the possibility of using data previously collected from an already existing cohort of patients and their parents. And finally, despite the potential recruitment challenges imposed by the lockdown and the rare nature of these diseases, we managed to reach our sample size.

Nevertheless, this study also had limitations. Firstly, as mental health screening is part of routine assessment among the CF and PCD population, during our inclusion period the PHQ-9, GAD-7 and BRS were submitted to all patients (100%), whereas the COVID-19-specific questionnaires were not (79%). Secondly, pre-pandemic mental health screening was not available for all participants (79%), which reduced the sample size. A larger sample size would increase statistical power of our analyses and improve their generalizability. Thirdly, by using online questionnaires, there might have been a difference between conditions in which participants filled in the surveys, which may have led to a response bias.

Despite these limitations, this study still provides a good indication of the impact of COVID-19 on depression, anxiety and resilience among the Dutch CF- and PCD-population in a single center. Future studies should focus on the evaluation of long term effects of the COVID-19 pandemic on the mental health of patients (and their parents) with CF or PCD.

The results of this study emphasize the importance of mental health screening and psychological care in PwCF and PwPCD and their caregivers remain as prevalence of symptoms of depression and anxiety in this population is high.

**CONCLUSION**

This study demonstrated high levels of symptoms of depression and anxiety among adolescents, adults and caregivers of individuals with CF or PCD, with an increase in depression scores for PwCF and an increase in anxiety scores in CF caregivers during the pandemic. Resilience was within the normal range. This study emphasizes the need for mental health screening for early detection of depression and anxiety symptoms and psychological treatment in PwCF and PwPCD and their caregivers.

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**APPENDIX**

*Translations to Dutch of the COVID-19 Exposure and Family Impact Scale (CEFIS).*

**COVID-19 Exposure and Family Impact Scale**

**COVID-19 Familie Impact Vragenlijst**

**versie voor ouders/verzorgers**

**Deel 2.** Corona heeft mogelijk veel impact gehad op u en uw gezinsleven. Wat voor invloed heeft corona gehad op de volgende gebieden in uw leven?

26. Ouderschap

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

27. Hoe familieleden met elkaar overweg kunnen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

28. Het vermogen om voor uw kind met [voeg ziekte/aandoening toe] te zorgen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

29. Het vermogen om voor andere kinderen in uw gezin te zorgen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

30. Het vermogen om te zorgen voor ouderen of mensen met een handicap binnen uw familie

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

31. Uw lichamelijke gezondheid – lichaamsbeweging

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

32. Uw lichamelijke gezondheid – eetpatroon en voeding

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

33. Uw lichamelijk gezondheid – slapen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

34. Uw emotionele gezondheid – angstklachten

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

35. Uw emotionele gezondheid – stemming

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

36. Over het algemeen, hoeveel last heeft u ervaren door corona?

Geen last 1 2 3 4 5 6 7 8 9 10 Extreme last

37. Over het algemeen, hoeveel last hebben uw kinderen ervaren door corona?

Geen last 1 2 3 4 5 6 7 8 9 10 Extreme last

**COVID-19 Exposure and Family Impact Scale for Adolescents and Young Adults (CEFIS-AYA)**

**COVID-19 Familie Impact Vragenlijst**

**versie voor adolescenten/jong volwassenen**

**Deel 2.** Corona heeft mogelijk veel impact gehad op jou en je gezinsleven. Wat voor invloed heeft corona gehad op de volgende gebieden in jouw leven?

30. Hoe gezinsleden met elkaar overweg kunnen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

31. Hoe je omging met je gezondheid

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

32. Onafhankelijk kunnen zijn

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

33. Kunnen zorgen voor anderen in je gezin

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

34. Je lichamelijke gezondheid – zittend gedrag (weinig bewegen, veel stilzitten achter de TV of andere schermen)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

35. Je lichamelijke gezondheid – lichaamsbeweging en sport

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

36. Je lichamelijke gezondheid – eten

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

37. Je lichamelijke gezondheid – slapen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

38. Je lichamelijke gezondheid – middelengebruik (roken/inademen van schadelijke stoffen, bijv. d.m.v. vape of e-sigaret, alcoholgebruik, wietgebruik etc.)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

39. Je emotionele gezondheid – angstklachten of zorgen

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

40. Je emotionele gezondheid – stemming

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

41. Je emotionele gezondheid – eenzaamheid

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

42. Je sociale leven – relaties met vrienden

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

43. Je sociale leven – romantische relaties of daten

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| ☐ 1. Sterk verbeterd | ☐ 2. Een beetje verbeterd | ☐ 3. Een beetje verslechterd | ☐ 4. Sterk verslechterd | ☐ Niet van toepassing |

44. In het algemeen, hoeveel last heb je ervaren van corona?

Geen last 1 2 3 4 5 6 7 8 9 10 Extreme last

*The COVID-19 questionnaire*

**5. Algemene coronavragen**

De volgende vragen gaan over de ziekte veroorzaakt door het coronavirus.

Omcirkel het antwoord dat het beste bij u past.

**1. Ik vermoed dat ik corona heb gehad** Ja Nee

**2. Ik heb een coronatest ondergaan.**  Ja Nee

**2b. *Indien ja*: De uitslag van de test was positief.** Ja Nee

**3. Mijn kind heeft vermoedelijk corona gehad** Ja Nee

**4. Mijn kind heeft een coronatest ondergaan.** Ja Nee

**4b. *Indien ja*: De uitslag van de test was positief.** Ja Nee

**5. Hoe zou u uw psychische gezondheid nu beschrijven, ten opzichte van voor corona?**

Achteruit gegaan Gelijk gebleven Vooruit gegaan

**Over het algemeen zijn mijn somberheidsklachten toegenomen tijdens corona.**

Helemaal niet mee eens Niet mee eens Neutraal Mee eens Helemaal mee eens

**Over het algemeen zijn mijn angstklachten toegenomen tijdens corona.**

Helemaal niet mee eens Niet mee eens Neutraal Mee eens Helemaal mee eens