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Critical disease burdens of Australian adults with cystic fibrosis: Results from an online survey

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Abstract

Background: The objective of this study was to conduct a web-based questionnaire to investigate self-reported phenotypes and disease burdens of individuals living in Australia and diagnosed with cystic fibrosis (CF) using a case–control study design.

Methods: An online questionnaire was distributed to individuals with CF and healthy control subjects. Overall health rating, medications, family history, education, clinical indicators of disease, and symptoms, including their severity and frequency, were evaluated.

Results: There was a total of 119 respondents consisting of 59 people living with CF and 60 controls. The CF cohort had significantly lower tertiary educational levels compared to controls. The analysis specific to the CF cohort depicted a significant correlation between the frequency of hospitalizations and the level of education in the CF cohort. Of the 26 self-reported symptoms of CF that were analyzed, 14 were significantly higher in the people living with CF. The CF cohort reporting symptoms of chronic pain (25%) described an increase in the burden of disease, depicting a 30% longer mean hospitalization, increased consumption of medications and significant relationships with four other symptoms, including muscle aches, digestive issues, pancreatic insufficiency, and abdominal swelling.

Conclusions: The nationwide survey identified a diverse range of clinical manifestations experienced by the Australian CF population. Chronic pain, linked to aging and the changing landscape of disease, was a significant indicator of the burden of disease. A comprehensive understanding of the phenotypic profiles and symptom variability will contribute to future research and provide insights into the impacts of disease and the burden of therapy, particularly in children, at the start of their health journey.

KEYWORDS

burden of disease, CFTR, cystic fibrosis, online survey, symptom perception

1 | INTRODUCTION

Cystic fibrosis (CF) is a chronic, debilitating and life-limiting autosomal recessive genetic disorder that occurs primarily in the Caucasian population or populations of European descent.[1] Affecting over 100,000 individuals worldwide, with the highest prevalence in Ireland, Australia, and North America, respectively, it is considered the most common life-threatening genetic condition globally.[2,3] CF is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes for chloride channels located on the apical membrane of epithelial cells.[4]

CF is a complex, multifaceted disorder affecting the respiratory and digestive systems most critically but with multisystemic involvement.[5] With variable disease severity and a broad clinical spectrum of manifestations, CF has a complex phenotype that reflects the underlying pathologies of the organs, tissues and systems affected.[6] The most prominent clinical manifestations observed include chronic pulmonary infections leading to bronchiectasis and progressive pulmonary failure, exocrine pancreatic insufficiency, intestinal obstruction, chronic hepatobiliary disease, and male infertility.[7] However, phenotypic variation is still substantial. The variation of this phenotypic expression is attributed to three interacting factors: environmental, genetic, and healthcare-related.[8]

Over recent decades, the life expectancy and prognosis for individuals diagnosed with CF have increased dramatically.[9] Improved treatment and management plans have led to increased survival and the need to predict disease outcomes other than lung transplantations or mortality.[10] According to the Australian Cystic Fibrosis Data Register (ACFDR), the survival age has been increasing over time, whereby the median age of death is currently 31 years.[11] Despite this projected increase in median survival age and the discovery of sophisticated therapies, quality of life is still limited due to significant clinical, psychological, psychosocial, and economic burdens.[12] With increased life expectancy, predicting the prognosis of the patient's disease, such as progression and severity, is critical to the patient's quality of life treatment options, adherence, and psychological health.[13]

Although international CF registries consistently update clinical data, the patient-reported phenotypic manifestations and clinical problems that individuals perceive or experience have not been well reported in the existing literature.[14] Patient-reported outcome measures (PROMs), or any report of the patient's health status directly from the patient, play a critical role in assessing symptoms and are widely utilised to support clinical decision-making and evaluate the effects of interventions.[15] In an era of CF modulators and genomic research, PROMs are critical to appraising these new therapies in addition to supporting people living with CF who are not eligible for modulator therapy.[16] Furthermore, PROMs provide a clear picture of the burden of disease, particularly in older people living with CF, whereby the landscape of the disease is changing.[17]

This study reports results from a case–control questionnaire aiming to investigate and analyze the various self-reported phenotypic manifestations and to characterize the disease burden for the CF population.

2 | METHODS

2.1 | Survey design and development

The questionnaire was designed and developed in conjunction with the research team (A.W., R.M., N.R., J.A.), an external reviewer, a statistician, and an anonymous CF specialist from Cystic Fibrosis Australia. The target population was individuals living with CF in Australia aged 18–60. The study was approved by the Southern Cross University Human Research Committee (Ethics Approval Number: 2021/105). This paper is reported using the Checklist for Reporting Results of Internet E-Surveys (CHERRIES).[18]

The questionnaire began with a detailed participant information sheet, including who should complete the questionnaire and how long it would take. Information was provided about the availability of the research results, the dissemination of the results and the anticipated value for future research.

The research team used the implied informed consent model, and the risks of completing the questionnaire were acknowledged in the information sheet. The questionnaire was identified as anonymous, and the research responsibilities involving confidentiality and privacy were outlined.

The questionnaire included 23 questions based on several themes impacting the burden of disease, including demographics, education level, hospitalizations, clinical symptoms and their severity and frequency, medications and family history of CF (see Supporting Information for the survey). Responses included multiple-choice options or free text boxes, allowing quantitative and qualitative responses to be collected. Items concerned with physical manifestations or symptoms were conditionally displayed based on the chosen response to other items. Item responses were either in the form of a simplistic 5-point Likert scale or visual analog.

2.2 | Recruitment

The research team utilised an open online survey that could be completed by people living with CF visiting the Cystic Fibrosis Australia website or identified on social media platforms such as Facebook, Instagram, and Twitter. The survey provided using the Qualtrics software platform (https://www.qualtrics.com) was activated and remained open for a period of 5 weeks (September 1, 2021 to October 7, 2021) on Cystic Fibrosis Australia's research and advocacy webpage. The control questionnaire (provided in the supplemental materials) was distributed on an unrelated page via social media.

A sample size of 118 based on the power of 90% was required to be statistically significant, and there are currently 1854 people living

with CF over the age of 18 in Australia, according to the Australian Cystic Fibrosis Data Registry (2020).

2.3 | Statistical analysis

The response information and data were downloaded from the Qualtrics Survey Platform and collated as tables in MS Excel format. The data were subsequently cleaned to remove missing values and analyzed using IBM SPSS for Windows (Version 28.0), a predictive analytical software package to explore the significance of the study. Descriptive statistics were used to describe data and provide means and standard deviation (SD) for analyzed variables. The multiple-choice response frequencies were summarised descriptively using percentages. For inferential statistics, continuous variables such as participants' demographics of age and body mass index (BMI), and clinical characteristics, such as the number of medications, were compared utilising independent *t*-tests. The assumption of independence for the *t*-tests was via the study design, with the participant's data collected once per variable. The assumption of normal distribution was confirmed by ensuring the groups' sample size was >30 (allowing the central limit theorem to approximate the normal distribution of sample means). The assumption of homogeneity of variance was met as Levene's statistic was nonsignificant at $p \geq 0.05$.

Tests of significance between categorical variables were analyzed using the chi-square method, and frequencies were described in percentages. The assumption of independence was also met due to the study design. The assumption that the expected frequency count was greater than five was checked by assessing the cross-tabulation tables in the SPSS outputs. If the $p < 0.05$ significance level, then the null hypothesis (no significant difference between the CF vs. non-CF groups) was rejected.

We hypothesized that certain responses might differ according to demographic characteristics (i.e., levels of education, gender), health status or type of mutation. Categorical variables were analyzed using the chi-square method, and where data counts were less than five, a Fisher's exact test was performed. All data were stored securely and held in compliance with the ethics committee and SCU's institutional requirements.

2.4 | Participant feedback

The survey's information and inclusion criteria were visually summarised in a pictorial information sheet and publicised with thanks to Cystic Fibrosis Australia via their webpage (Communique-338-LAY-OF-THE-LAND-Surveys) social media and official announcements or "Communique." It was also uploaded to two CF support group pages on social media, where respondents could click on an anonymous link. Those who had indicated they would be interested in future research conduct and had provided an email address or contact number were emailed directly.

3 | RESULTS

3.1 | Response rate of the study sample

Once the survey was activated, 165 people (92 people living with CF and 73 in the control group) accessed the survey. Forty-two stopped at page 1, which was the participant information sheet and inclusion criteria. Of the remaining, 64% ($n = 59$) of individuals with CF and meeting the inclusion criteria fully completed the questionnaire, whereas 82% ($n = 60$) of control respondents met the inclusion criteria and completed the survey. The average time taken by people living with CF to complete the questionnaire was 13.65 min compared to the control group, which took an average of 5 and 20 s.

Most responses were obtained from the first 3 days of the survey being released online through Cystic Fibrosis Australia. The response data suggests that the use of reminder messages and new posts online or "retweets" successfully created engagement and increased the respondent sample size for both cases and controls over the 5 weeks. A large portion of respondents, precisely 72 of 111 (64.9%), expressed their interest in future research participation and provided contact details. Table 1 describes the demographic data.

TABLE 1 Demographic analysis of individuals living with cystic fibrosis (CF) and healthy controls ($n = 119$).

Respondent characteristic	Individuals living with CF		Healthy controls		*p* Value
	Count	Mean ± SD	Count	Mean ± SD	
Gender					
Female	37 (64%)		50 (83%)		
Male	21 (36%)		10 (17%)		
Age		39.2 ± 11.1		36.8 ± 10	0.314
Height (cm)		167.6 ± 9.8		168.6 ± 7.8	0.064
Weight (kg)		67.3 ± 16.1		73.8 ± 21.3	0.198
BMI (kg/m^2)		23.7 ± 4.3		25.8 ± 6.4	0.036*

*$p < 0.05$.

3.2 | Respondent characteristics

The demographics and anthropometrics of the respondents are summarised in Table 1. There were no significant differences in age between CF and controls. There was a significant difference in the gender proportions, with significantly more females in the healthy control group compared to CF ($p = 0.016$). Compared to controls, the CF cohort had significantly lower BMI measurements, but there was no difference in height. Based on BMI, 3% ($n = 2$) of the CF cohort were underweight, 69% ($n = 41$) were considered in the healthy weight range, 15% ($n = 9$) were overweight, and 12% were classified as obese ($n = 7$).

The CF population consisted of various birth origins but was predominantly Australian, with 52 respondents (88%). Portugal 2% ($n = 1$), the Netherlands 2% ($n = 1$), New Zealand ($n = 2$), Papua New Guinea 2% ($n = 1$), England 2% ($n = 1$), and Slovakia 2% ($n = 1$) were included in countries of birth. In the control group, 63% ($n = 38$) were born in Australia, 19% ($n = 11$) were born in Ireland, 2% ($n = 1$) in America, 2% ($n = 1$) in Switzerland, 7% ($n = 4$) in England, 2% ($n = 1$) in Lithuania, 2% ($n = 1$) in Scotland, and 2% ($n = 1$) in New Zealand.

There was a significant difference in the education level of the two groups ($p = 0.032$), as described in Figure 1, whereby the CF cohort reported having lower levels of higher education. There was no significant difference between males and females in the CF cohort in reference to levels of education ($p = 0.131$); however, of the 17 respondents who reported having a postgraduate degree, 82% ($n = 14$) were female. When analyzing the significance of education levels and burden of care, there were higher odds of being hospitalized for individuals with lower levels of education ($p = 0.037$) (odds ratio = 3.738, 95% confidence interval [1.042, 13.417]).

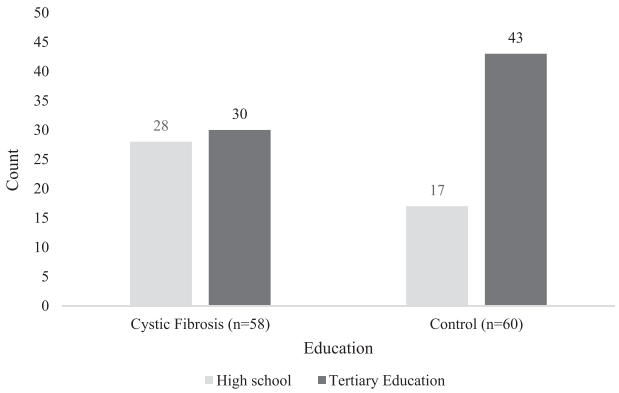

FIGURE 1 Levels of education in cystic fibrosis (CF) patients in comparison with control patients ($n = 118$).

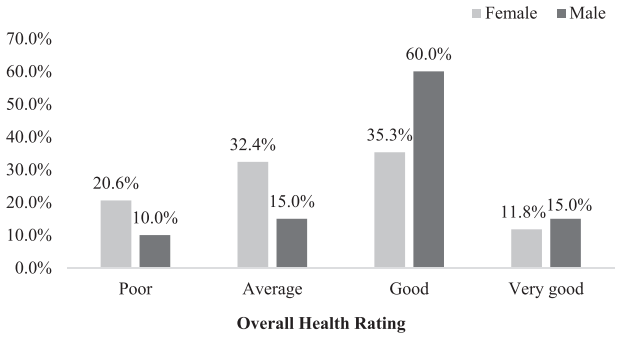

FIGURE 2 Comparison of overall health rating between genders in the cystic fibrosis cohort.

3.3 | Respondent's health characteristics and burden of disease

The mean age for diagnosis of CF was 6.2 ± 12.3 years (range = 0–52). The modal age diagnosed was at birth consisting of 50% ($n = 30$) of the responses. The most common genotype described was homozygous F508del at 49.2% ($n = 29$), followed by heterozygous F508del at 28.8% ($n = 17$). "Other" mutations consisted of G85E, G542X, G551D, and W1282X ($n = 6$; 10%). 96.6% ($n = 57$) of respondents knew their mutations compared to 1.7% ($n = 1$) who said they did not. There was one missing data point for genotype.

No respondents in the CF population said they were diagnosed with another genetic disease. Three participants chose "prefer not to say," and there was one missing data point. When both samples were asked to describe their overall health, the majority of people living with CF's most common response was "Good" and "Average," while more participants in the control group rated their health as "good" and "very good." A chi-square test was conducted to test if there would be a difference in self-reported health status. There was a significant difference in health perception between the two groups ($\chi^2 = 11.102$, df = 3, $p = 0.011$).

In relation to hospitalizations in the last year, 42% ($n = 23$) of CF participants reported they had been hospitalized with a mean (±SD) duration of stay of 16 (±SD) days. Comparatively, 13% ($n = 8$) of the control group were hospitalized in the last year ($\chi^2 = 11.825$, df = 1, $p = <0.001$). The CF respondents also identified that they visited their GP or healthcare practitioner on average "Every month" compared to the controls who answered "Every year." The CF patient's gender was also investigated for significance in health status, whereby females had a higher response rate when describing their status as "poor" ($n = 8$) compared to males ($n = 2$), as described in Figure 2.

Fifty-one respondents living with CF responded to the question pertaining to medication consumption, whereby eight items were missing. A total of 86% of the CF respondents ($n = 45$) reported taking medication with a mean (SD; range) quantity of 10.51 (6.933; 1–30) medications currently. Six respondents reported taking no medications. Of the participants who responded "yes" to currently taking medication, 52% ($n = 22$) were currently prescribed a CFTR modulator therapy which included Symdeko (tezacaftor/ivacaftor and ivacaftor) ($n = 8$), Ivacaftor ($n = 2$), Trikafta (elexacaftor, tezacaftor, and ivacaftor) ($n = 5$), and Orkambi (lumacaftor and ivacaftor) ($n = 7$), and 81% ($n = 34$) were taking pancreatic enzymes (Creon). In gender

analyses in the CF cohort, there was a trend towards, but no significant difference in the mean (SD) number of medications consumed by females compared to males (11.14 (5.534) vs. 9.21 (9.308), $t(41) = 0.85$, $p = 0.053$). In the last year, 64% ($n = 38$) reported taking antibiotics for various infections such as *Pseudomonas aeruginosa*, *Aspergillus*, *Nontuberculous mycobacterium*, *Staphylococcus aureus*, *Burkholderia cepacia*, and *Haemophilus influenzae*. A total of 58% ($n = 34$) of people living with CF reported being diagnosed with a *Pseudomonas aeruginosa* infection. People living with CF's age of *Pseudomonas aeruginosa* diagnosis ranged from 1 to 38 years (mean ± SD, 15.44 ± 9.430 years). The modal response was at age 10.

Forty-nine people living with CF (83%) responded having relatives diagnosed with CF, with the modal answer being that their siblings were affected.

Equal percentages of 46% for both people living with CF ($n = 27$) and controls ($n = 28$) reported having a family history of cancer. There was no significant relationship between a family history of cancer and CF ($\chi^2 = 1.251$, df = 2, $p = 0.535$). Relative to the diagnosis of COVID-19, 1.7% ($n = 1$) of people living with CF reported being a confirmed case of COVID-19 compared to 1.7% ($n = 1$) of controls. The CF cases reported "moderate" severity levels compared to the control, who reported "mild" symptoms.

When the people living with CF were asked if they would like to access more personalised information or use their genetic profile to guide information about their disease, 45.8% ($n = 27$) responded that they would like to access more personalised information. A smaller percentage of 8.5% ($n = 5$) said they would not, and 28.8% ($n = 17$) were unsure, as described in Figure 3.

3.4 | Patient-reported symptoms

When reporting the presence of the 26 major patient-reported symptoms, there were 114 (54 people living with CF and 60 controls) total responses. Five data points were missing from the CF cohort. People living with CF reported having an average of four symptoms or health concerns listed.

Comparatively, 40% ($n = 24$) of the healthy control group reported having "no problems." The mean number of symptoms

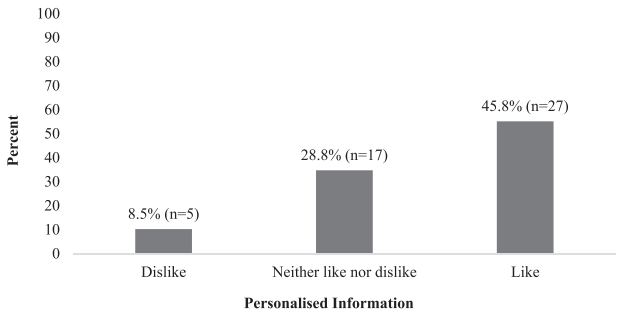

FIGURE 3 Interest in access to more personalised information about their phenotype, genetic profile, and expected disease progression ($n = 49$).

was one for those who reported having health issues (range 0–5). The control group's most common response to health concerns was "Back and neck problems,", at 23% ($n = 14$). Thirteen respondents living with CF included "Other" problems such as hypothyroidism, headaches and dizziness, medication side effects, polycystic ovarian syndrome, lactose intolerance, gluten sensitivity, asthma, post-traumatic stress disorder, and early onset menopause. Two respondents living with CF specifically reported depression and anxiety. Three controls reported "other" manifestations, including endometriosis, Graves' disease, and anxiety.

Results from individual chi-square tests performed comparatively between the people living with CF, and the control group are described in Table 2. When further analyzing the patient-reported symptoms, specifically between the genders in the CF cohort, eight symptoms were reported as statistically significant for female CF respondents, as detailed further in Table 3.

3.4.1 | Chronic pain in CF

As shown in Table 2, 25% of people living with CF ($n = 15$) reported chronic pain. This cohort had an increased mean age of 44 (SD 12) compared to those without pain (mean age of 37). A one-way ANOVA revealed that there was a statistically significant difference in mean age according to chronic pain status ($f(1, 52) = [4.163]$, $p = 0.046$). Severity was also increased with age (mild mean age of 44, SD 5, moderate mean age of 44, SD 10 and severe mean age of 49, SD 12). A one-way ANOVA depicted the mean age of the first bacterial infection was significantly younger in the cohort who reported chronic pain at age 10 compared to 18 ($f(404.149, 2530.233) = [5.111]$, $p = 0.031$).

An analysis of the variable chronic pain described significant relationships with three other symptoms, including muscle aches ($\chi^2 = 8.124$, df = 1, $p = 0.004$), digestive issues ($\chi^2 = 10.083$, df = 1, $p = 0.001$), and abdominal swelling ($\chi^2 = 6.297$, df = 1, $p = 0.012$).

The survey was well-received, and the response quality was high, with participants, both CF and control, providing detailed descriptive text responses when prompted. It also depicted that utilising an online platform such as social media is feasible for sensitive topics and a platform to share experiences. The sample size, although limited, was greater than what would have been possible to interview individuals due to COVID-19 restrictions; it prevented cross-infection and allowed participants the time and opportunity to reflect on their answers without pressure and maintain anonymity

4 | DISCUSSION

This case–control study, utilising patient-reported symptoms, identified significant high disease burdens, including treatment burden, CF comorbidities and high healthcare resource usage. Notably, in addition to the already well-established clinical manifestations such as respiratory, gastrointestinal or nutritional manifestations of CF, to

TABLE 2 Comparison of self-reported symptoms of individuals living with cystic fibrosis (CF) and healthy controls (n = 119).

System	CF patients (n = 59) n (%)	Control group (n = 60) n (%)	Total (n = 119) n (%)	Pearson Chi-square	p Value
Nervous					
Chronic pain	15 (25.42)	5 (8.33)	20 (16.80)	7.428	0.006*
Musculoskeletal					
Arthritis/rheumatism	7 (11.86)	4 (6.67)	11 (9.24)	1.292	0.256
Back or neck problems	11 (18.64)	14 (23.33)	25 (21)	0.146	0.703
Fractures, bone/joint injury, or bone disease	5 (8.47)	2 (3.33)	7 (5.88)	1.732	0.188
Muscle aches	14 (23.73)	7 (11.67)	21 (17.65)	3.845	0.050
Respiratory					
Lung disease	42 (71.18)	4 (6.67)	46 (38.65)	59.712	<0.001*
Persistent cough	34 (57.63)	4 (6.67)	38 (31.93)	41.995	<0.001*
Asthma	20 (33.89)	12 (20)	32 (26.89)	4.259	0.039*
Bronchitis/lung disease	24 (40.68)	0	24 (20.17)	34.487	<0.001*
Recurring pulmonary infection	25 (42.37)	0	25 (21.00)	36.357	<0.001*
Hearing problems	7 (11.86)	2 (3.33)	9 (7.56)	3.624	0.057
Eye/vision problems	6 (10.16)	6 (10)	12 (10.08)	0.037	0.847
Cardiovascular					
Heart problems	3 (5.08)	0	3 (2.52)	3.423	0.064
Stroke problems	1 (1.69)	0	1 (0.84)	1.121	0.290
Hypertension/high blood pressure	6 (10.16)	5 (8.33)	11 (9.24)	0.252	0.616
Hematology					
Anemia or iron deficiency	15 (25.42)	7 (11.67)	22 (18.49)	4.737	0.030*
Gastroenterology					
Food malabsorption/ other digestive issues	28 (47.46)	6 (10)	34 (28.57)	27.93	<0.001*
Abdominal swelling	22 (37.29)	6 (10)	28 (23.53)	14.906	<0.001*
Pancreatic insufficiency	43 (72.88)	3 (5)	46 (38.65)	77.642	<0.001*
Endocrine					
Diabetes	20 (33.89)	3 (5)	23 (19.32)	18.113	<0.001*
Liver and bile duct	8 (13.56)	0	8 (6.72)	9.560	0.002*
Urinary					
Kidney disease	4 (6.78)	0	4 (3.36)	4.606	0.032*
Immune					
Autoimmune disease	2 (3.39)	2 (3.33)	4 (3.36)	0.012	0.915

System	CF patients (n = 59)n (%)	Control group (n = 60)n (%)	Total (n = 119) n (%)	Pearson Chi-square	p Value
Oncology					
Cancer	3 (5.08)	0	3 (2.52)	3.423	0.064
Reproductive					
Fertility issues	21 (35.59)	2 (3.33)	23 (19.33)	22.786	<0.001*

*p < 0.05

TABLE 3 Comparative analysis of the self-reported symptoms between individuals living with cystic fibrosis (CF) genders (n = 59).

System	Female	Male	Total (n = 59) n (%)	Count		Severity		Frequency	
				Pearson chi-square	p Value	Pearson chi-square	p Value	Pearson chi-square	p Value
Nervous									
Chronic pain	11	4	15 (25.42)	0.958	0.328	1.137	0.566	3.733	0.155
Musculoskeletal									
Arthritis/rheumatism	5	2	7 (11.86)	0.288	0.591	2.222	0.329	0.750	0.687
Back or neck problems	11	0	11 (18.64)	8.126	0.004*				
Fractures, bone/joint injury, or bone disease	3	2	5 (8.47)	0.021	0.885	4.000	0.046	1.333	0.513
Muscle aches	13	1	14 (23.73)	7.243	0.007*			3.611	0.057
Respiratory									
Lung disease	31	11	42 (71.18)	9.535	0.002*	5.486	0.064	3.111	0.211
Persistent cough	26	8	34 (57.63)	8.220	0.004*			7.601	0.107
Phlegm and mucus* amount and* color	26	8	34 (57.63)			11.769	0.008*	12.914	0.012*
Asthma	16	4	20 (33.89)	4.191	0.041*	6.161	0.046	0.323	0.570
Bronchitis	19	5	24 (40.68)	5.230	0.022*	1.624	0.444	0.873	0.646
Recurring pulmonary infection	18	7	25 (42.37)	1.797	0.180				
Vestibular									
Hearing problems	5	2	7 (11.86)	0.247	0.619	3.733	0.155	2.100	0.350
Optical									
Eye/vision problems	4	2	6 (10.16)	0.040	0.842	3.000	0.083	3.750	0.153
Cardiovascular									
Heart problems	1	2	3 (5.08)	1.196	0.274	0.750	0.386	3.000	0.086
Stroke problems	1	0	1 (1.69)	0.599	0.439				
Hypertension/high blood pressure	1	5	6 (10.16)	6.204	0.013*	5.000	0.025*	1.875	0.171
Hematology									
Anemia or iron deficiency	12	3	15 (25.42)	2.585	0.108	8.775	0.012*	1.197	0.550
Gastroenterology									
Food malabsorption/other digestive issues	20	8	28 (47.46)	1.787	0.181	0.430	0.806	0.836	0.658
Abdominal swelling	18	4	22 (37.29)	6.021	0.014*	0.309	0.857	0.433	0.805

(Continues)

TABLE 3 (Continued)

System	Female	Male	Total (n = 59) n (%)	Count Pearson chi-square	Count p Value	Severity Pearson chi-square	Severity p Value	Frequency Pearson chi-square	Frequency p Value
Pancreatic insufficiency	28	15	43 (72.88)	0.659	0.417	6.049	0.049*	3.126	0.209
Diabetes	14	6	20 (33.89)	0.675	0.411	6.510	0.039*	6.462	0.040
Liver and bile duct	5	3	8 (13.56)	0.001	0.977	2.000	0.368		
Urinary									
Kidney disease	2	2	4 (6.78)	0.311	0.577	1.333	0.248	4.000	0.046
Immune									
Autoimmune disease	2	0	2 (3.39)	1.222	0.269				
Oncology									
Cancer	2	3	3 (5.08)	0.019	0.891	3.000	0.083		
Reproductive									
Fertility issues	11	10	21 (35.59)	1.211	0.271	4.906	0.086		

*$p < 0.05$.

name a few, up to a quarter of adults with CF reported suffering from chronic pain. Furthermore, the research also identified the emerging trends of weight gain and obesity in the aging CF population. This trend is depicted in the CF respondents, whereby 27% of the cohort were classified as overweight and obese. There was no significant difference in weight between the CF cohort and the controls, whereas historically, CF has been associated with low-fat mass and malnutrition.

It is well-recognised that individuals living with CF have a high disease burden in areas such as hospital and health service utilisation and a wide range of clinical manifestations of the respiratory, gastrointestinal, endocrine, and reproductive systems. Our study not only reports the known symptoms and burdens of CF but also the severity and frequency of the exacerbations in addition to the patient's reported perception of their health. As extensively detailed in the literature, patient-reported outcomes measures and feedback are critical in assessing the quality of care and evaluating clinical outcomes. The patient-reported feedback from this research is consistent with this rationale in that it provides a clear picture of the research gap and disease burdens that currently exist, particularly for older people living with CF, such as chronic pain.

This study demonstrated that chronic and acute pain is common in CF adults and has significant implications for patient assessments or diagnoses, medical management, and clinical outcomes. Pain is a critical feature in the patients' overall clinical profile, and this study demonstrates that chronic pain should be included as a hallmark symptom and an integral component of CF treatment. This is the first investigation into self-reported chronic pain and the associated severity and frequency to date. The prevalence of chronic pain was significantly higher in the CF group, with both increased frequency and severity levels. Notably, severity levels rose with mean age, indicating that it is a factor congruent with aging or potentially therapy use, whereby future studies are required. One quarter (25%) of the CF cohort reported chronic pain, which was also significantly related to other symptoms such as muscle aches, digestive issues, and abdominal swelling. Of the limited data available, particularly noting a lack of evidence in the last 10 years, our findings differ from the published historical literature in that the survey respondents reported abdominal pain as the primary location for pain.[19] Previously abdominal pain was frequently more common in the pediatric population. Widespread reporting of pain in the cohort was not surprising and can potentially be attributed to the multitude of abdominal pathologies, interactions of new modulator therapies and an increasing prevalence of gastrointestinal cancers.

The study results describe a significant proportion of people living with CF reporting gastrointestinal disturbances such as pain, abdominal swelling, digestive issues, gastroesophageal reflux, and malabsorption. Frequency and severity levels were high, with 30% (n = 8) of the people living with CF reporting constant severe digestive issues. As described in the literature and depicted in the research results, people living with CF consume an abundance of varying medications; however, little research has been conducted on their effects on the hepatobiliary or digestive system.[20]

Of this cohort who responded to having chronic pain, there was a significant difference in BMI, with the chronic pain cohort having an increased BMI, an older mean age, a younger age of first bacterial infection, an increased amount of medications and an increased number of days hospitalized inferring a significant burden of disease, not just on the individual, but also on the healthcare system. Higher pain average scores are associated with significant interference with restriction of activities and work, respiratory symptoms, sleep disturbances, higher levels of depression and anxiety, and poor health-related quality of life (HRQoL).[21] Pain also caused increased

difficulty in performing regular therapeutic strategies such as physical therapy and thus influenced adherence to therapy.

There is currently a lack of information in the literature on not only treating pain in CF but also evaluating and monitoring it. In addition, there is a lack of the patient's perspective on pain; therefore, there is a significant risk that patients feel unrecognised or unheard. Recent research has investigated the top priority research questions from the CF community, who indicated through consumer-led steering committees and workshops that their top two priorities included effective ways of simplifying treatment burden and the relief of gastrointestinal symptoms, including pain.[22] The study also described qualitative interviews describing the interference in schoolwork due to pain. As indicated in 2017,[22] pain is a research priority for people living with CF, yet there is a complete lack of evidence or research to date. Future longitudinal studies with greater statistical power are required to fully explore the impacts of pain both mentally and physically. Greater efforts are required to develop practical, evidence-guided approaches to assess the prevalence and impact of pain, particularly on its effects on HRQoL, physiological, and psychological health.

To the authors' knowledge, based on the author's literature review at the time of writing, our study is also the first to report on the level of education attained in conjunction with health status and phenotypic characteristics of CF. People living with CF that had received higher tertiary education training had fewer hospitalizations indicating how the burden of disease may impact education and potentially subsequent income and employment opportunities. A recent study reported that educational levels influenced individuals' HRQoL scores, and those that had received higher education scored statistically better scores in every domain.[23] Stofa et al. hypothesized that a work environment provided social scaffolding, and therefore CF individuals could cope better with their disease.[23] This hypothesis could also be related to the response to the question pertaining to access to more personalised information, whereby the individuals with higher education significantly reported wanting more personalised information for their future disease progression.

As described, CF is a multifaceted complex disorder. People living with CF are impacted by numerous confounding factors such as environmental, lifestyle, genetic and therapeutic interactions that influence disease severity and progression. The current challenges faced by stakeholders in developing and implementing CF care globally are substantial. Yet, numerous opportunities exist for superior care, better health outcomes and decreased burden of institutionalized health care for individuals living with CF. Clinical manifestations of psychological and physiological symptoms should be included, and detailed records should be maintained to create a longitudinal descriptive study of the CF journey both from the clinician's and the patient's perspective. Furthermore, recommendations would also be to include the research priorities in the national data set and consistently analyze and evaluate through patient engagement if they feel that their priorities have been acted upon.

5 | LIMITATIONS AND STRENGTHS

A number of strengths can be observed in this study due to the online nature of the questionnaire. Research in the current pandemic can be challenging; thus, conducting a case–control study online can improve the study's statistical power while maintaining infection control in a vulnerable population. Questionnaires are also easily collected once engagement with the relevant stakeholders has been successfully established.

Limitations of this study included the small sample relative to the Australian CF population. As described by the ACFDR, 1854 adults with CF live in Australia over the age of 18. Relative to the population of Australian people living with CF, the number of respondents to the questionnaire was small ($n = 59$), depicting 3.2% of the Australian CF population. However, recent research using online surveys in the United Kingdom reported the same difficulty in recruiting people living with CF, citing low respondent rates in multiple studies across the United Kingdom.[24] Similar to these statistics, Cystic Fibrosis Australia conducted a survey to explore the research and advocacy priorities for 2020 and received 102 consumer responses. In addition, 54 participants were recruited for a "Think Tank." Therefore, the recruitment of the CF community globally is challenging.

When analyzing the statistical significance of severity and frequencies between cases and controls, there were limited numbers, and therefore future research is required with sufficient statistical power. Similar to the first limitation, the control sample also lacked statistical power. Future recommendations to mitigate this would be to open the survey for control participants simultaneously.

The questionnaire, being an online survey, was also subject to self-selection bias, self-reported patient data, internet accessibility, and digital literacy requirements. Self-selection and self-reporting information provide important self-perception aspects for the participants, however, recommendations for future research would be to recruit participants online and via dedicated CF clinics or specialists. This would help to mitigate the self-reported data limitation so that physical health, such as infection types, could be cross-checked with healthcare practitioners. Overall, clinical data gathered from healthcare practitioners would add to the rigour of future studies in this area. It is also recommended that questions about mental health status be included. Information specifically detailing the burden of anxiety or depression of individuals with CF would benefit future studies as these are major modifiers of the CF experience.

The control group had a significantly larger proportion of female respondents due to convenience sampling from social media groups concerning health. To mitigate any gender biases, future studies should include gender matching in both cohorts.

Further limitations of the study include the timing of the study, whereby several surveys involving people living with CF were being conducted simultaneously. Potential survey saturation and respondent fatigue may have affected the sample size. The survey timing also coincided with multiple lockdowns during the COVID-19

pandemic. This could have caused bias in the number of hospitalizations as individuals reported using "hospital in the home" options.

6 | CONCLUSION

CF and the associated phenotypic symptoms or comorbidities present numerous significant interpatient variations in clinical manifestations from birth to adulthood. Currently, the landscape of CF is rapidly changing due to the availability of modulator therapies. This study is the first national survey to be published describing self-reported disease severity and frequency of clinical exacerbations in the same genotype. Furthermore, it reports chronic pain as a significant burden of disease. It is also the first study that correlates higher education levels with a decreased disease burden. With novel research investigating the effects of new treatment options and modifier genes on disease severity and progression, it is imperative to relate better, more specific phenotypes to the inherited CF genotypes. The prolonged survival of individuals living with CF demands attention not only to the clinical manifestations they are presenting with but to their overall quality of life. The pediatric population is especially vulnerable as children may have difficulty expressing and understanding their symptoms. Consequently, the evidence from this study could guide new ways of improvement in clinical assessments of children living with CF. Future research where genomic data is collected in addition to clinically reported outcomes and patient-reported symptoms is imperative to explore and comprehensively understand the disease burden.

AUTHOR CONTRIBUTIONS

Anastasia Ward: Conceptualization; writing—review and editing; writing—original draft; formal analysis; investigation; project administration; data curation; visualization; methodology; validation. **Ramil Mauleon:** Conceptualization; writing—review and editing; formal analysis; supervision; methodology; software; investigation; validation; data curation. **Jacinta Arellano:** Conceptualization; writing—review and editing; formal analysis; supervision; investigation; methodology; validation. **Chee Y. Ooi:** Writing—review and editing; formal analysis; supervision; validation; visualization. **Nedeljka Rosic:** Conceptualization; writing—review and editing; formal analysis; supervision; investigation; methodology; visualization; validation; project administration; software.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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