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The prevalence of developmental defects of enamel in a cohort of adults with cystic fibrosis – A cross sectional study

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ABSTRACT

Objectives: Cystic Fibrosis is an autosomal recessive condition. It is a multisystem disease treated with a broad range of pharmacological therapies, diet and nutrition, and physiotherapy. Previous studies suggest that people with cystic fibrosis have a higher prevalence of developmental defects of enamel which may place this population at a greater risk of developing oral diseases such as caries. The aim of this study was to assess a cohort of people with cystic fibrosis (PwCF) for the presence of developmental defects of enamel and compare the results with a control group of people without cystic fibrosis.
Methods: A cross sectional study involving 92 participants with cystic fibrosis and 92 controls was conducted in Cork University Dental School & Hospital. All participants completed a detailed questionnaire prior to undergoing a full clinical examination. The Developmental Defect of Enamel Index was used as a measurement index. All data was statistically analysed with the help of statisticians from Cystic Fibrosis Registry of Ireland.
Results: 64 % (n = 59) of PwCF had enamel defects compared to just 30 % (n = 28) of people without cystic fibrosis. The median number of teeth affected by enamel defects in the study group was 1.5, compared to 0 in the control group.
Conclusion: In this study the cohort of PwCF had more enamel defects than people without CF. Further research is required to investigate the aetiology of these findings.
Clinical significance: Clinicians should be vigilant after teeth have erupted in PwCF as they may have an increased susceptibility to developmental defects of enamel.

1. Introduction

Cystic fibrosis (CF) is an autosomal recessive condition caused by a mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is a multisystem disease associated with abnormalities in salt and water transport across epithelial surfaces [1]. It is estimated that 162,428 people live with the condition worldwide [2]. Ireland has the highest global incidence of CF with 1 in 1353 live births annually [3]. It is thought that 1 in 19 Irish carry a copy of the altered gene responsible for causing the disease [4]. Studies have shown a higher prevalence of developmental defects of enamel (DDE) in people with CF [5–7]. Enamel is produced by highly specialised cells called ameloblasts and defects in enamel are deficiencies of formation. The initial stages of enamel formation involve the secretion of matrix proteins such as amelogenin, ameloblastin, and enamelin. The latter stages involve the mineralisation and maturation of matrix proteins to form enamel [8]. Ameloblasts are 'finite', meaning they do not continue to produce enamel throughout an individual's lifespan. Once a tooth is fully formed, ameloblasts cease their activity and are lost during tooth eruption such that enamel cannot be naturally replaced if damaged or lost. The specialised pathways involved in enamel formation are controlled by genetics and influenced by epigenetic and environmental factors such as systemic illness, infections, medications, trauma, and radiation. Disruptions to these pathways may result in disturbances to the quantity and /or quality of

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enamel known as enamel hypoplasia and hypomineralisation respectively [8,9].

Clinically enamel hypoplasia presents as pits and grooves in the tooth surface, and yellowish-brown stains where the underlying dentine is showing through due to thin or missing enamel. Hypomineralised enamel is of normal thickness but is not fully mineralised therefore the enamel can appear opaque, creamy white or discoloured. Opacities may be diffuse and/ or demarcated. Individuals with DDE may experience hypersensitivity, aesthetic concerns, increased risk of caries, and premature tooth wear. Psychological well-being and oral health related quality of life have been shown to be influenced by aesthetic perception of teeth affected by the discolouration and tooth morphology associated with DDE [10]. From a clinician's perspective, teeth with DDE can be challenging to anaesthetise and restorative bonding to altered enamel can be unpredictable. Early diagnosis and preventive care are essential for the successful management of DDEs. Therefore, the identification of specific illnesses and medications that may predispose individuals to DDEs is important for the development of specialised treatments that can be targeted for specific populations. The objective of this cross-sectional study was to assess a cohort of people with cystic fibrosis (PwCF) for the presence of developmental defects of enamel and compare the results with a control group of people without cystic fibrosis. Our null hypothesis states that adults with cystic fibrosis do not have an increased prevalence of developmental defects of enamel when compared to a cohort of adults without cystic fibrosis.

2. Materials and methods

2.1. Ethical approval

The study design was submitted to and given full ethical approval by the Clinical Ethics Committee of the Cork Teaching Hospitals (ECM 03/ 2022 PUB). The study was conducted in compliance with the principles of the Declaration of Helsinki and written informed consent was obtained from each participant.

2.2. Recruitment

This cross-sectional study included 92 PwCF and 92 controls without CF. The study group included adults with cystic fibrosis who were attending the adult cystic fibrosis unit in Cork University Hospital (n = 180). In order to achieve the highest number of recruitments, all individuals attending the unit for their routine health check were invited to participate in the study. As this was a single centre study of a rare disease, the aim was to be as close to a consensus as possible for this centre, and a coverage rate of 55.5 % was achieved from this centre. A population-based control group was recruited. Control participants were invited to attend Cork University Dental School & Hospital for a free dental examination. Advertisements for recruitment were placed in local shopping centres, community centres, and on social media channels linked to the study. Telephone and email contact details of the study co-ordinator were provided. Prior to appointment allocation, a negative CF diagnosis and no known familial diagnoses were confirmed via telephone screening by a study co-ordinator. No financial rewards were offered to study participants. Patients were seen during the COVID-19 pandemic, between September 2020 and October 2022. The study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting case–control studies.

2.3. Inclusion and exclusion criteria

The inclusion criteria for entering the study group:

- Individuals with a positive cystic fibrosis diagnosis ≥18 years as confirmed by previous sweat and genetic tests
- Individuals residing in Ireland

The inclusion criteria for entering the control group:

- Individuals with a negative cystic fibrosis diagnosis ≥18 years
- Individuals residing in Ireland
- Systemically healthy with no long-term medication

The exclusion criteria for this study:

- Individuals on long term medication
- People with a family history of CF

2.4. Data collection and oral examination

Each participant was given a questionnaire data collection form to complete with assistance from a research assistant prior to undergoing a dental examination. The questionnaire recorded age, gender, education, cystic fibrosis status, smoking and alcohol consumption, diet and dietary habits, fluoride exposure, oral health and hygiene practices, aesthetic concerns, and medication. The questionnaire used was the World Health Organisation's *'Oral Health Questionnaire for Adults*' [11] and the remaining questions were devised following discussion with patient advocates from Cystic Fibrosis Ireland. Prior to conducting the study examiners underwent training and calibration. For training, examiners were provided with a manual outlining study protocols and examination criteria. Examiners reviewed a collection of photographic slides that illustrated enamel defect criteria. The examiners reviewed these materials independently and then successfully completed a simulated calibration examination using a separate series of photographs overseen and calibrated against a gold standard examiner. Dental examinations were performed by two trained and calibrated examiners (FO'L & NC) equipped with a plane surface mouth mirror (mirror head size 4, front), a WHO community periodontal index probe and a Daray lamp light source. Study participants were examined within a single examination room in the adult CF unit in Cork University Hospital to reduce risk of cross infection of CF pathogens such as *Pseudomonas aeruginosa* between patients. Control participants were examined in a standard dental operatory in Cork University Dental School & Hospital. Enamel defects were recorded using the Developmental Defects of Enamel Index [12]. Using this index, the changes in enamel, in this case are classified into six categories; Demarcated Opacity, Diffuse Opacity, Hypoplastic Enamel and their combinations Demarcated/Diffuse, Demarcated/Hypoplastic and Diffuse/Hypoplastic. Additional information collected as part of this study was caries prevalence (DMFT/DMFS index), periodontal condition (CPI modified index), and oral hygiene status (Oral Hygiene Index of Greene–Vermillion). The aforementioned data are reported in separate publications.

2.5. Statistical analysis

Before beginning the study, the two examiners were calibrated for the DDE Index recorded. Intra- examiner reproducibility was measured as 0.95 by the kappa statistic indicating a high inter-rater reliability.

Study participant characteristics were summarised using median (interquartile range) for continuous variables, and frequency (percentage) for categorical variables. The CF, and non-CF groups were compared using Wilcoxon rank sum tests, Chi-sq tests or Fisher's exact tests where appropriate.

Total DDE scores were calculated by adding the number of teeth with DDEs present. A negative binomial regression model was fitted for DDE total including the effects of CF status, gender, age and look of teeth and their interactions.

A chi-square test was used to test if proportion of individuals with DDE in the aesthetic zone, and hypoplastic enamel defects were statistically different between groups.

An alpha level of 5 % was used for all tests to determine when the difference was statistically significant (p<0.05). R version (4.2.0) was

used for all statistical analysis.

3. Results

The study group consisted of a total of 92 participants, 57 % were male ($n = 52$) and 43 % were female ($n = 40$). The control group ($n = 92$) consisted of 53 % female ($n = 49$) and 46 % male ($n = 43$). The median age for study group and control group participants was 31 years and 27 years, respectively. The percentage of participants who had any experience of an enamel defect was 64 % ($n = 59$) of study participants and 30 % ($n = 28$) of control group participants. The median number of teeth affected by enamel defects in the study group was 1.5, compared to 0 in the control group. Table 1 outlines the characteristics of STUDY participants.

There were 64 % of the CF group affected by enamel defects, compared with 30 % of the non-CF group. Table 2 summarises the output from the three negative binomial models fitted. Model 1 shows

Table 1
Characteristics of study participants. Median and interquartile range (IQR) are presented for continuous variables, and the CF and non-CF groups are compared using the Wilcoxon rank sum test. Frequency and percentage are presented for categorical variables, and the CF and non-CF groups are compared using Chi-sq tests (or Fisher's exact test where frequencies are less than 5).

		CF ($n = 92$)	Non-CF ($n = 92$)	p-value
Gender	Male	52 (56.5 %)	43 (46.7 %)	0.238
	Female	40 (43.5 %)	49 (53.3 %)	
Median Age in years (IQR)		31 (25.0–35.8)	27 (23.0–33.0)	0.044
Education	Primary	1 (1.2 %)	2 (2.2 %)	
	During Secondary	2 (2.3 %)	2 (2.2 %)	
	Secondary	25 (29.1 %)	23 (25 %)	
	Third level	58 (67.4 %)	65 (70.7 %)	0.889
Smoking		1 (1.1 %)	7 (7.6 %)	0.078
Alcohol use		67 (76.1 %)	68 (74.7 %)	0.964
Diet and Dietary Habits	3 or less meals per day	10 (11.2 %)	36 (39.1 %)	
	4 or 5 meals per day	59 (66.3 %)	49 (53.3 %)	
	6 or 7 meals per day	17 (19.1 %)	6 (6.5 %)	
	More than 7 meals per day	3 (3.4 %)	1 (1.1 %)	<0.001
Sugary Drinks	None	5 (5.6 %)	19 (20.7 %)	
	Once a day	26 (29.2 %)	45 (48.9 %)	
	Twice a day	28 (31.5 %)	22 (23.9 %)	
	3 times a day	14 (15.7 %)	5 (5.4 %)	
	4 times a day or more	17 (18.9 %)	1 (1.1 %)	<0.001
How do your Teeth affect your ability to chew your food	1	81 (92.0)%	84 (91.3 %)	
	2	7 (8.0)%	6 (6.5 %)	
	3	0 (0 %)	2 (2.2 %)	0.5663
Fluoride exposure	Toothpaste has fluoride	71 (79.8 %)	88 (95.7 %)	
	Toothpaste has no fluoride	0 (0 %)	2 (2.2 %)	
	Unsure	18 (20.2 %)	2 (2.2 %)	<0.001
Tooth brushing	Twice a day or more	67 (72.3 %)	85 (92.4 %)	
	Once a day or less	22 (24.7 %)	7 (7.6 %)	0.003
Aesthetic concerns	Not at all	38 (42.7 %)	54 (58.7 %)	
	Affects me	51 (57.3 %)	38 (41.3 %)	0.0451
Medication	Osteoporosis	9 (10.2 %)	0 (0 %)	
	Osteopenia	8 (9.1 %)	6 (6.5 %)	
	No	71 (80.7 %)	86 (93.5 %)	0.002
	Bisphosphonates	10 (11.6 %)	0 (0 %)	<0.001
	Nutritional supplements	17 (19.1 %)	1 (1.1 %)	<0.001
	Antibiotics	1 (1.3 %)	0(0 %)	0.918

Table 2
Negative Binomial regression analysis of CF associated with total number of teeth with DDE for three models. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Total number of Teeth with DDE prevelance ratio (95 % CI)		Model 1	Model 2	Model 3
CF Status		5.604 (3.349–9.436) ***	4.942 (2.758–8.968) ***	6.505 (3.71–11.623) ***
Age			0.966 (0.933–0.999)*	0.973 (0.939–1.007)
Gender	Female		1.096 (0.657–1.832)	0.707 (0.414–1.197)
Diet and Dietary Habits	4 or 5 meals per day		1.013 (0.508–1.97)	0.676 (0.026–18.077)
	6 or 7 meals per day		1.037 (0.394–2.778)	1.27 (0.607–2.87)
	More than 7 meals per day		2.517 (0.549–17.683)	0.676 (0.337–1.418)
Sugary Drinks	Once a day		1.252 (0.503–3.061)	
	Twice a day		1.854 (0.724–4.668)	
	3 times a day		2.077 (0.675–6.444)	
	4 times a day or more		1.295 (0.409–4.203)	
Fluoride exposure	Toothpaste has no fluoride			0.707 (0.414–1.197)
	Unsure			0.676 (0.026–18.077)
Tooth brushing	Once a day or less			1.27 (0.607–2.87)
Aesthetic concerns	Affects me			0.676 (0.337–1.418)

Note: Model 1: CF status as the independent variable. Model 2: Model 1 plus demographic variables. Model 3: significant predictors from model 2 plus health factors.

that those with CF have a 5.6 times higher prevalence of DDE in teeth compared to the non-CF group, and this is statistically significant, ($p<0.001$). Model 2 looks at demographic and behavioural variables and when these are included the CF group have a higher number of DDE compared to the non-CF 4.9, which is statistically significant, ($p<0.001$). Model 3 looks at dental health parameters and any significant demographic variables. The number of DDE in those with CF is statistically higher than the non-CF group, 6.5, ($p<0.001$). (Fig. 1)

The prevalence of the enamel defect by type e.g., demarcated opacity, diffuse opacity was analysed. The results are shown in Figs. 2 and 3.

A total of 44 people in the study group were affected by demarcated opacities, compared to 15 people in the control group. Twenty-five people and 18 people experienced diffuse opacities and hypoplastic enamel defects respectively in the study group. Only eight people in the control group displayed diffuse opacities and hypoplastic defects.

A total of 164 teeth in the study group and 28 teeth in the control group displayed demarcated opacities. Diffuse opacities were the second most common type of enamel defect present, affecting 74 teeth in the study group and 15 teeth in the control group. Forty-five teeth in the study group experienced hypoplastic defects, compared to 10 teeth in the control group. Demarcated hypoplastic, and diffuse hypoplastic enamel defects were both seen in the study group but not in the control group. Teeth in the aesthetic zone (tooth number 13–23 in the upper

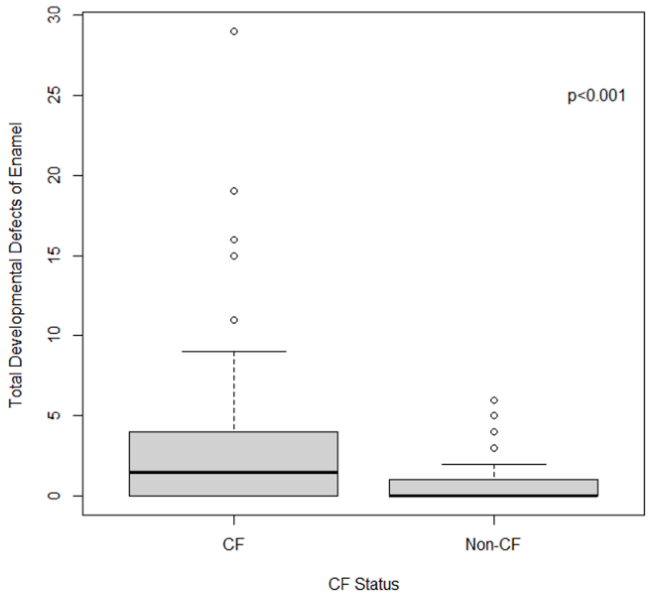

Fig. 1. Boxplot of number of teeth with DDE by CF status.

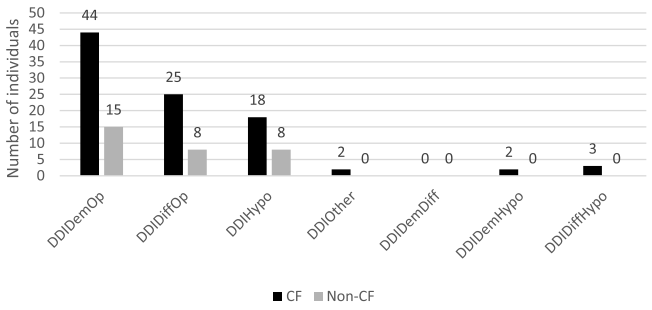

Fig. 2. Total number of participants according to CF status affected by DDE type ($n = 92$). DemOp (Demarcated Opacity), DiffOp (Diffuse Opacity), Hypo (Hypoplastic Enamel), DemDiff (Demarcated/Diffuse), DemHypo (Demarcated/Hypoplastic), and DiffHypo (Diffuse/Hypoplastic).

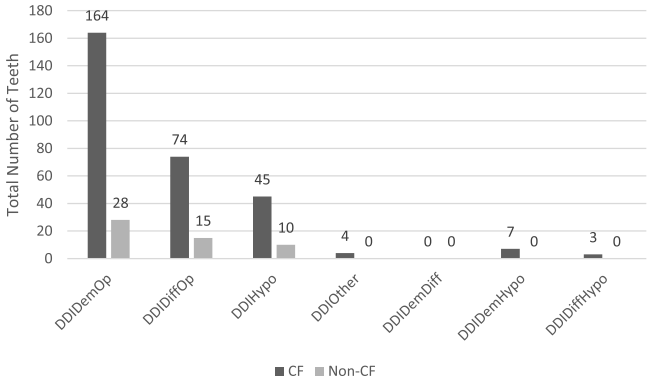

Fig. 3. Total number of teeth with each DDE type. DemOp (Demarcated Opacity), DiffOp (Diffuse Opacity), Hypo (Hypoplastic Enamel), DemDiff (Demarcated/Diffuse), DemHypo (Demarcated/Hypoplastic), and DiffHypo (Diffuse/Hypoplastic).

arch and 33–43 in the lower arch) [13] were most affected by enamel defects (43 %), followed by molars (35 %), and lastly premolars (21 %). This differed slightly in the control group, in which molars were most commonly affected (43 %), aesthetic zone teeth (38 %), and premolars (19 %). A Chi-square test confirmed a statistically significant difference in the presence of DDE in the aesthetic zone between the CF and Non-CF group. A p-value of <0.001 was recorded. (Tables 3 and 4).

18.5 % of people with CF and 9.8 % of control participants had hypoplastic enamel defects. A chi-squared test revealed that there was not a significant difference in the mean number of teeth with caries between those with hypoplasia and those without. A *p*-value of 0.235 was recorded.

4. Discussion

Previous studies investigating the prevalence of developmental defects of enamel in people with CF have primarily included children and adolescents with adults forming a small portion of study populations [5–7,14–19]. The majority of these studies can now be deemed historic. This study is the largest global study to assess oral health in adults with cystic fibrosis. Study strengths include the use of a standardized measurement index, the Developmental Defect of Enamel index and a population-based control group. Whilst differences in study recruitment and measurement indices make comparisons with previous data more challenging there is a consistent pattern that PwCF have more DDE [5–7, 14–18]. Only one previous study reported no difference between study group and control groups [19]. However, this study included siblings of individuals with CF in the control group who may be in receipt of a dysfunctional CFTR gene thus influencing results.

One recent study by Pawlaczyk-Kamieńska et al. [7] offers comparable results to our study. They reported a higher prevalence of enamel defects ($p = 0.03$) among a cohort of 22 adults with CF compared to an age and gender matched control group without CF. Similar to findings by Pawlaczyk Kamieńska et al. [7] this study noted a statistically significant difference in the number of enamel defects in PwCF($p<0.001$) therefore the null hypothesis was rejected. Previous studies do not report on the variable of gender and how this may influence defect prevalence. Our study found no significant difference in the prevalence of enamel defects between males and females regardless of their CF status ($p = 0.801$). Similar to Pawlaczyk-Kamieńska et al. [7], the enamel defects recorded were not limited to one group of teeth but were distributed across all tooth types, however in this study teeth within the aesthetic zone were most affected in PwCF.

The most common type of enamel defect noted in this study in PwCF was demarcated opacities ($n = 44$), closely followed by diffuse opacities ($n = 25$). Both demarcated and diffuse opacities are qualitative disturbances of enamel which typically occur during the maturation phase of enamel formation. The maturation phase involves the transport of calcium and phosphate ions into the developing enamel, enzyme secretion to facilitate the increase in mineral density, and pH regulation to assist mineral precipitation [20]. The maturation phase is highly regulated and can by disrupted by both environmental and genetic insults. Unlike other systemic conditions associated with developmental defects of enamel such as celiac disease or nephrotic syndrome in which the ethology of enamel defects is understood, the ethology of enamel defects in PwCF is not. Recent animal model studies have reported enamel pathology as a result of the loss of function in the CFTR gene [21] while former studies have attributed enamel defects to chronic illness and antibiotic use [13]. Dysfunction of the CFTR gene results in ionic imbalance of epithelial secretions in multiple organ systems, thus it is reasonable to assume that dysfunction of the CFTR gene may be associated with developmental defects of enamel. As previously mentioned qualitative and quantitative disturbances of enamel can predispose teeth

Table 3
Prevalence of DDE in Aesthetic zone for CF and Non-CF.

	CF $N = 92$ (%)	Non-CF $N = 92$ (%)	Chi-square p-value
DDE Present in Aesthetic Zone	41 (44.6 %)	14 (15.2 %)	<0.001

Table 4
Prevalence of hypoplastic enamel defects for CF and Non-CF.

	CF $N = 92$ (%)	Non-CF $N = 92$ (%)	Chi-square p-value
hypoplastic enamel defects	17 (18.5 %)	9 (9.8 %)	<0.001

to dental caries, premature tooth wear, erosion [22]. As part of a wider study assessing oral health, caries levels were also recorded. This study did not find an increase in dental caries in participants with hypoplastic enamel defects ($p = 0.236$). Enamel defects were most prevalent in the aesthetics zone of study participants ($p < 0.001$) There was a significant difference in the concern over aesthetic appearance between the two groups ($p = 0.002$), with participants in the study group reporting aesthetic concern. This concern was a primary reason for conducting this study following PPI involvement during study design. The pharmacological management of CF has changed dramatically since the introduction of gene modulator therapy in 2012. Gene modulators are designed to correct the malfunctioning protein made by the CFTR gene; they address the underlying cause of the disease [23]. These therapies reduce symptom burden and improves clinical metrics and quality of life for PwCF. All but three previous studies assessing the prevalence of enamel defects in PwCF were conducted prior to the introduction of gene modulator therapies in 2012. Studies including this current study and those conducted after the introduction of gene modulator therapy [7,17,18] included individuals who would not have been prescribed these medications at the time of tooth development and formation. It is reasonable to assume that if enamel defects in this population are linked to chronic illness, antibiotic use, and CFTR dysfunction there should be a decrease in the incidence of enamel defects in future generations of individuals with cystic fibrosis who have early access to genetic modulators.

While this study was a relatively large study when one considers the rarity of the disease, the sample size was small therefore it can be difficult to draw conclusions from such a limited sample size or compare our studies to others using systematic review techniques. Therefore, it would be beneficial to conduct a multi-centre study. Not only would this increase sample size it would also permit comparison of CF genotype, phenotype, social, demographic, and treatment modalities. The study population was self-selecting which in itself is a limitation. There was likely to be a degree of self-selection bias. For example, dental phobic patients may not have participated and PwCF may not have participated due to apprehension seeing another healthcare professional during the Covid-19 pandemic. A further limitation of the study was the absence of examiner blinding, this was not possible due to examination of study group participants within the CF unit. The study was initially designed to examine all participants under the same operatory session however due to Covid-19 a pragmatic decision was made to examine the patients with CF in the setting of the CF unit where they had a separate entry and exit to the rest of the hospital. Thus, minimising their exposure to a location with potentially high exposure risk to Covid-19. The study lacks objective photographic documentation of the enamel defects which is a limitation. Again, to minimise exposure of vulnerable PwCF to healthcare professionals, appointment times were kept as short as possible therefore photographs were not taken. The authors appreciate in a population of adults DDE may have been previously restored. Therefore, we may have been under estimating the number of DDE and overestimating filled teeth in our caries study. In this study no attempt was made to differentiate lesions that fall into patterns that may represent molar incisor hypomineralisation or fluorosis and no weight was given to certain DDE which may result in dental disease like hypoplastic lesions.

5. Clinical significance

Restorative dental treatment required for dental caries, tooth wear and poor aesthetics places a large burden on healthcare expenditure. The impact of poor oral health and poor aesthetics on self-esteem, quality of life and emotional well-being has been well documented [24]. Early recognition of developmental defects of enamel and comprehension of their clinical implications is vital. Clinicians should be vigilant after teeth have erupted in PwCF as they may have an increased susceptibility to developmental defects of enamel. Preventative strategies and early intervention for dental pathology associated with enamel defects should help to reduce oral disease and reduce the burden of care for both PwCF and healthcare professionals; our study confirms a higher number of enamel defects in PwCF. Ideally, dentists should form part of a multidisciplinary team to ensure PwCF receive appropriate education, prevention, and dental treatment. Furthermore, it highlights the importance of future research in the area of oral health particularly in light of the evolving pharmacological management of the disease.

CRediT authorship contribution statement

FionaO'Leary: Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **Niamh Coffey:** Data curation, Methodology. **Francis M Burke:** Writing – review & editing. **Anthony Roberts:** Writing – review & editing. **Paul O'Regan:** Formal analysis, Software, Writing – review & editing. **Laura Kirwan:** Formal analysis, Software, Writing – review & editing. **Barry Plant:** Conceptualization. **Martina Hayes:** Conceptualization, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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