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Prevalence, risk factors and outcomes of cardiac disease in cystic fibrosis: a multinational retrospective cohort study

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People living with cystic fibrosis may be at increased risk of cardiac disease as they grow older. Further work is needed to better understand risk factors and risk profiles in more detail. https://bit.ly/3D5Zvxr

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Abstract

Background Although people living with cystic fibrosis (PwCF) often have some risk factors for cardiovascular disease, including diabetes and chronic inflammation, little is known about the long-term cardiac risk in this condition. We aimed to determine the characteristics, rates and outcomes for cardiac disease in CF.

Methods We looked at rates and outcomes for cardiac disease in 5649 adult PwCF in the UK CF Registry and 6265 adult PwCF in TriNetX (a global federated database of electronic healthcare record data). We used propensity matching to compare risk of major adverse cardiac events (MACE) (myocardial infarction, left-sided heart failure and atrial fibrillation) in PwCF against matched non-CF comparators in the general population and other inflammatory diseases.

Results PwCF had a high prevalence of diabetes but low rates of hypertension and obesity. Some cardiac risk factors (age, diabetes and hypertension) were associated with MACE, but relationships between disease-specific risk factors (lung function and intravenous antibiotic days) were also observed. In propensity score-matched analyses, PwCF had higher risk of MACE than matched general population comparators (hazard ratio (HR) 1.65, 95% CI 1.40–1.95; p<0.001) and an equivalent or higher relative risk compared with other inflammatory conditions considered "high risk" for cardiovascular disease, including systemic lupus erythematosus (HR 0.95, 95% CI 0.82–1.09; p=0.44), rheumatoid arthritis (HR 1.21, 95% CI 1.00–1.48; p<0.001) and HIV (HR 0.93, 95% CI 0.82–1.06; p=0.29).

Conclusions PwCF are at increased risk of adverse cardiac disease events. Future work should focus on defining determinants of cardiovascular risk such that appropriate risk stratification can be employed.

Introduction

Recent therapeutic advances in cystic fibrosis (CF) include the development of CF transmembrane conductance regulator (CFTR) modulators, which effectively restore CFTR function in >90% of the CF population [1], and survival is likely to increase significantly [2].

With increasing survival, there are concerns that cardiac disease may represent a "time bomb" for people living with CF (PwCF) [3]. PwCF may have a number of risk factors for cardiac disease, including diabetes, high salt intake and chronic kidney disease [4, 5], and additionally, chronic inflammation, a hallmark of CF, has been shown in other inflammatory diseases (*e.g.* systemic lupus erythematosus (SLE), rheumatoid arthritis and HIV) to be associated with excess cardiac risk [6–8].

A low body mass index (BMI), low hypertension prevalence, altered lipid metabolism and low rates of smoking have historically been considered to explain the absence of high rates of cardiac disease in PwCF, which until recently has been considered rare. However, in the face of increasing survival, increasing BMI and increased fat absorption associated with CFTR modulators, the long-term risk for PwCF is unclear [9].

An understanding of the epidemiology and outcomes of cardiac events in PwCF is therefore needed. The aim of this study was to investigate cardiac disease epidemiology and outcomes in PwCF using multisource patient data registries.

Methods

Data sources and analysis

Retrospective cohort studies were performed in two datasets. The UK CF Registry was first established in 1995 and includes anonymised longitudinal clinical and demographic data on over 12 000 PwCF, with >99% coverage of the UK CF population. Cardiac outcomes were first included in 2016. Data is recorded annually by CF clinical teams. TriNetX is a healthcare data network with real-time access to anonymised electronic healthcare records from over 70 healthcare organisations internationally but predominantly within North America. Data within the platform include demographics, International Classification of Diseases, 10th Revision (ICD-10) disease codes, procedures (ICD-10 Procedure Coding system), medication details (rxNorm/Veterans affairs National Formulary codes) and laboratory measurements (coded as Logical Observation Identifiers Names and Codes (LOINC)). Data regarding lung function and annual antibiotic usage were only available in the UK CF Registry,

Study population

Adults (⩾18 years old in 2016) with CF were included for analysis in both datasets. In the UK CF Registry, only those with annual review data in 2016 were included. In the UK CF Registry, data were available from 2016 (when cardiac outcomes were first recorded) with 5 years of data up to the most recent data release from 2020. In TriNetX, all adults with a hospital (inpatient or outpatient) encounter in 2016 were included for analysis, with outcomes censored at 5 years. Throughout, comorbidities and outcomes were defined by presence of a single ICD-10 code, except for CF itself (given the validity and generalisability of ICD-10 code-based research in CF is unclear) [10]. To optimise a CF definition we combined hospital encounters and frequency of CF (ICD-10 E84) codes into a cohort definition to more precisely identify PwCF. Mandating a hospital encounter and four or more instances of an ICD-10 code for CF defined a cohort that closely resembled those seen in well-validated sources such as the UK CF Registry and US CF Foundation Registry (supplementary figure S1). Those without any codes for CF were considered the non-CF general population cohort. For comparisons of CF against other inflammatory diseases, individuals with SLE, rheumatoid arthritis and HIV were identified by ICD-10 codes within TriNetX as previously described [11–13]. Comparisons between CF and other groups were only possible in TriNetX and not the UK CF Registry due to the single-disease nature of the UK CF Registry. Derivation of each group within TriNetX is described in figure 1 and supplementary figure S3. Throughout, clinical characteristics were recorded at index, which was 2016 for the UK CF Registry and the hospital encounter in 2016 for TriNetX.

Cardiac outcomes

Available cardiac outcomes were variable across datasets (supplementary figure S2). A core outcome set of major adverse cardiac events (MACE), including myocardial infarction, left-sided heart failure and atrial fibrillation, was available in each dataset and therefore formed a standardised composite outcome for comparison across datasets. A full list of ICD-10 codes utilised in the study is provided in the supplementary material.

Statistical analysis

UK CF Registry analyses were conducted in RStudio and TriNetX analyses were conducted within the TriNetX platform itself. All TriNetX analyses were conducted on 30 April 2023. Throughout, univariate analyses consisted of Chi-squared tests for categorical variables and independent samples t-tests for continuous variables. Missing data were only observed for LOINC variables, *e.g.* BMI (19.8% missing). Given these values were only used in a descriptive context, no imputations for missing data were performed. In the TriNetX platform, comparisons were made between PwCF against the general population and active disease controls (SLE, rheumatoid arthritis and HIV). Standardised mean differences were used to show the distribution of demographic and clinical data among the groups and calculated as the difference in the means or proportions of a particular variable divided by the pooled estimate of standardised differences for that variable. Propensity score matching consisted of a 1:1 matching by logistic regression. A greedy nearest-neighbour matching algorithm with 0.1 pooled standard deviations of

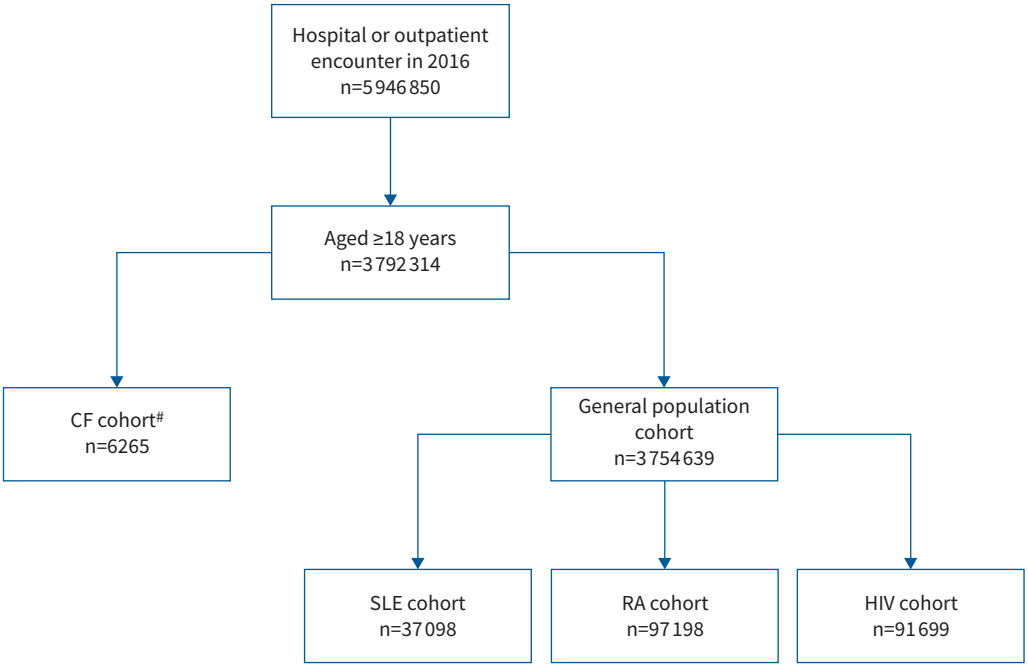

FIGURE 1 Cohort identification within the TriNetX dataset. CF: cystic fibrosis; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis. #: CF cohort defined by four or more instances of International Classification of Diseases, 10th Revision code E84.

the propensity scores in aggregate was used to balance potential differences in cohorts. Cohort matching was performed for established cardiac risk factors (diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease). Any baseline characteristic with a standardised mean difference <0.100 was considered well matched (details are provided in supplementary section E3). After propensity score matching, a Cox's proportional hazards model was used to compare the matched cohorts.

Results

Data were available for 5649 adult PwCF in the UK CF Registry (mean±SD age 32.1±11.0 years) and 6265 adult PwCF in TriNetX (mean±SD age 27.8±10.1 years). Baseline characteristics are presented in table 1. There were similarities between datasets: obesity was present in 309 (5.5%) and 338 (5.4%) of the cohort in the UK CF Registry and TriNetX, respectively, mean BMI was 23.1 and 24.4 kg·m^{-2}, respectively, but

TABLE 1 Baseline clinical characteristics of adults living with cystic fibrosis (CF) in the UK CF Registry and TriNetX datasets

	UK CF Registry	TriNetX
Subjects	5649	6265
Age (years)	32.1±11.0	27.8±10.1
Female	2549 (45.1)	3981 (63.5)
BMI (kg·m^{-2})	23.1±4.2	24.4±6.4
Hypertension	127 (2.2)	743 (11.8)
Hypercholesterolaemia	NA	65 (1.0)
Obesity (BMI >30 kg·m^{-2})	309 (5.5)	338 (5.4)
Family history of ischaemic heart disease	NA	195 (3.1)
Smoking	NA	126 (2.0)
Diabetes	1996 (35.3)	1675 (26.7)
Chronic kidney disease	88 (1.6)	333 (5.3)

Data are presented as n, n (%) or mean±SD. BMI: body mass index; NA: not available.

a lower prevalence of hypertension was observed in the UK CF Registry (2.2% *versus* 11.8%). There were more females in TriNetX (64% *versus* 45% in the UK CF Registry). Prevalence of diabetes was variable: present in 35.3% in the UK CF Registry but 26.7% in TriNetX.

MACE incidence and prevalence

At index within the TriNetX dataset there was a baseline prevalence for MACE in 151 (2.5%), annual incidence ranged from 0.8% to 2.6% and by 2020, MACE had occurred in 433 out of 6265 (6.9%). In the same study period, MACE was recorded for 89 out of 5649 (1.6%) in the UK CF Registry. Thus, annualised incidence was 1.3% and 0.3% for TriNetX and the UK CF Registry, respectively.

Characteristics of those with MACE

Characteristics of those with and without MACE are presented in table 2. In both the UK CF Registry and TriNetX, those with MACE were older and had a higher prevalence of hypertension and diabetes. High BMI and chronic kidney disease were also more prevalent in those experiencing MACE in TriNetX but not in the UK CF Registry. Those with MACE had poorer lung function and greater intravenous antibiotic use.

Risk of MACE in CF compared with the general population

We compared MACE between PwCF and matched comparators in the non-CF population within the TriNetX platform. Risk of MACE was significantly higher for PwCF (hazard ratio (HR) 1.75, 95% CI 1.59–1.92; p<0.001) (table 3). After successful propensity score matching of all 6265 PwCF, the increased risk of MACE remained (HR 1.65, 95% CI 1.40–1.95; p<0.001) and was driven largely by myocardial infarction (HR 2.13, 95% CI 1.66–2.73) (figure 2). This finding was consistent across unmatched analyses and also when only matched for age and sex (table 3 and supplementary table S1). We evaluated the validity of our primary analysis in sensitivity analyses exploring the impact of cardiac diagnoses prior to the study period and also the impact of elexacaftor/tezacaftor/ivacaftor availability towards the very end of the study period. In both analyses the primary analysis was found to be robust (supplementary tables S8 and S9).

Outcomes compared with other inflammatory diseases

We next explored MACE in other inflammatory conditions. To confirm the high cardiac risk associated with inflammatory conditions, we successfully propensity score matched 37 098, 97 198 and 91 699 people living with SLE, rheumatoid arthritis and HIV, respectively, with those from the general population

TABLE 2 Characteristics of people living with cystic fibrosis (CF) with comparison by major adverse cardiac events (MACE) in the UK CF Registry and TriNetX

	No MACE	MACE	p-value
UK CF Registry			
Subjects	5560	89	
Age (years)	31.9±10.8	46.4±14.7	<0.001
Female	2518 (45.3)	31 (34.8)	0.063
BMI (kg·m^{-2})	23.1±4.2	23.7±4.1	0.195
Obese	303 (5.4)	6 (6.7)	0.777
CF-related diabetes	1948 (35.0)	48 (53.9)	<0.001
Chronic kidney disease	88 (1.6)	0 (0.0)	0.444
Hypertension	120 (2.2)	7 (7.9)	0.001
FEV_1 (% pred)	63.3±14.7	54.4±23.6	<0.001
Pseudomonas aeruginosa	3155 (56.7)	56 (62.9)	0.422
Intravenous antibiotic use (days)	19.8±32.7	38.3±51.7	<0.001
TriNetX			
Subjects	5832	433	
Age (years)	27.5±10.2	33.2±10.1	<0.001
Female	3693 (67.9)	288 (66.5)	0.50
BMI (kg·m^{-2})	26.1±6.6	28.8±8.7	0.01
Obese	287 (4.9)	51 (11.8)	<0.001
Diabetes	1420 (24.3)	255 (58.9)	<0.001
Chronic kidney disease	219 (3.8)	114 (23.3)	<0.001
Hypertension	601 (10.3)	142 (32.8)	<0.001
Hypercholesterolaemia	55 (0.9)	10 (2.3)	0.007

Data are presented as n, n (%) or mean±SD. BMI: body mass index; FEV_1: forced expiratory volume in 1 s.

TABLE 3 Comparison of risk for cardiac disease between people living with cystic fibrosis (CF) and the general population

	Unadjusted analysis						Propensity score-matched analysis					
	CF	Events	Non-CF	Events	HR (95% CI)	p-value	CF	Events	Non-CF	Events	HR (95% CI)	p-value
MACE	6265	433	3 754 639	121 921	1.75 (1.59–1.92)	<0.001	6265	433	6265	215	1.65 (1.40–1.95)	<0.001
Myocardial infarction	6265	227	3 754 639	52 566	2.08 (1.82–2.37)	<0.001	6265	227	6265	86	2.13 (1.66–2.73)	<0.001
Heart failure	6265	129	3 754 639	48 144	1.31 (1.10–1.55)	<0.001	6265	129	6265	98	1.07 (0.82–1.39)	0.65
Atrial fibrillation	6265	148	3 754 639	49 233	1.48 (1.26–1.73)	<0.001	6265	148	6265	79	1.53 (1.16–2.01)	0.002

Data are presented as n, unless otherwise stated. HR: hazard ratio; MACE: major adverse cardiovascular events. Analyses conducted in TriNetX population only. Propensity score matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

(supplementary tables S3, S5 and S7). All three were associated with increased MACE (supplementary tables S3, S5 and S7). We then replicated the matching process but this time compared the three inflammatory conditions against CF (successfully matching 5223, 5901 and 6192 PwCF with SLE, rheumatoid arthritis and HIV comparators, respectively) (table 4). In CF, risk of MACE was equivalent to SLE and HIV (HR 0.95, 95% CI 0.82–1.09; p=0.44; and HR 0.93, 95% CI 0.82–1.06; p=0.29, respectively) and was greater than rheumatoid arthritis (HR 1.21, 95% CI 1.00–1.48). See supplementary tables S2, S4 and S6 for composite breakdown.

Discussion

We used two independent datasets to investigate cardiac disease in CF. Our main findings are that PwCF have a significantly higher risk of cardiac disease than matched counterparts in the general population. Furthermore, cardiac risk in PwCF was equivalent to or higher than other chronic inflammatory diseases considered "high risk" for cardiac disease.

Until recently, cardiac disease has been considered rare in CF. Early CF autopsy studies found normal coronary arteries in children who had died from CF and, more recently, pre-lung transplant angiograms were

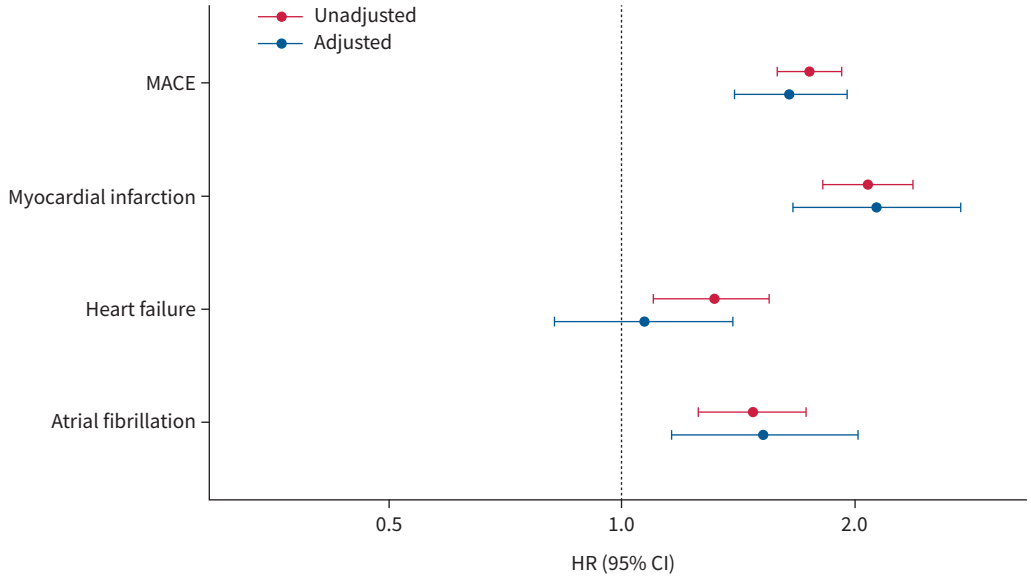

FIGURE 2 Hazard ratio (HR) for risk of major adverse cardiac events (MACE) in people living with cystic fibrosis *versus* general population comparators in unadjusted and adjusted analyses. Analyses conducted in TriNetX population only. Adjusted analyses were propensity score matched for cardiac risk factors (diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

TABLE 4 Comparison of risk for major adverse cardiac events between people living with cystic fibrosis (CF) and other inflammatory conditions

	Unadjusted analysis						Propensity score-matched analysis					
	CF	Events	Non-CF	Events	HR (95% CI)	p-value	CF	Events	Non-CF	Events	HR (95% CI)	p-value
Systemic lupus erythematosus	6265	433	37 098	3984	0.61 (0.56–0.68)	<0.001	223	385	5223	389	0.95 (0.82–1.09)	0.439
Rheumatoid arthritis	6265	227	97 198	4547	0.75 (0.66–0.86)	<0.001	5901	223	5901	177	1.21 (1.00–1.48)	0.055
HIV	6265	433	91 699	9173	0.67 (0.61–0.74)	<0.001	6192	430	6192	461	0.93 (0.82–1.06)	0.293

Data are presented as n, unless otherwise stated. HR: hazard ratio. Analyses conducted in TriNetX population only. Propensity score matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

reported to be normal in 14 adults with CF [14, 15]. However, these findings are unlikely to be generalisable to an increasingly older comorbid CF population where increased arterial stiffness and endothelial dysfunction, well-validated predictors of future cardiac disease, have been reported [16, 17]. Illustratively, the first case series of coronary artery disease in CF was recently published [18]. To the best of our knowledge, the present study is the first to describe cardiac adverse event morbidity in CF at a population level and the first to include comparisons with the general population or other inflammatory conditions.

Life expectancy for PwCF has progressively improved over recent decades, with a current median life expectancy of 53.3 years in the UK [19]. In the last few years highly effective disease-modifying drugs, *i.e.* CFTR modulators, have become available and are likely to herald an even greater increase in life expectancy. However, increasing age, BMI and a high prevalence of CF-related diabetes have generated concerns that PwCF may become high risk for cardiac diseases. The results from this study, conducted across two datasets before the widespread availability of CFTR modulators, suggest annualised MACE incidence ranges from 0.3% to 1.3%. Importantly, our findings demonstrated that PwCF are already at higher risk of MACE than the general population and suggest urgent work is needed to understand how this risk changes with CFTR modulator therapy.

Cardiac risk is usually determined by the presence of traditional risk factors, some of which, including diabetes and renal disease, are well appreciated in CF [20, 21]. Hypertension is a key risk factor for cardiac disease in the general population, but PwCF are thought to generally exhibit lower blood pressure due to salt losses related to CFTR dysfunction [22]. Accordingly, we found hypertension had a prevalence of 2–11% in adults with CF across datasets, much lower than the prevalence of ~25% in the UK adult population [23]. Hypertension was more prevalent in those with MACE, a consistent finding in both the UK CF Registry and TriNetX dataset, reinforcing the importance of hypertension as a risk factor for cardiac disease when present in CF. Similarly, diabetes is an important risk factor for cardiac disease and we found over half of people experiencing MACE had CF-related diabetes. Diabetes prevalence appeared variable between datasets, with 35.3% prevalence in the UK CF Registry but 26.7% in the TriNetX data. Given the poor prognostic outcomes of CF-related diabetes, early identification is a keystone of CF clinical care and as such is likely captured well within CF-specific disease registries like the UK CF Registry [24]. Conversely, CF-related diabetes does not have a specific ICD-10 code and therefore may be prone to under-reporting or misclassification in non-disease-specific, ICD-10-dependent datasets such as TriNetX. Historical geographic variation in the use of continuous glucose monitoring for the diagnosis of CF-related diabetes may also be a contributory factor [25]. Differences were also observed between groups where those with MACE had a higher prevalence of chronic kidney disease and obesity in TriNetX, but not in the UK CF Registry. This could reflect different population characteristics or regional definitions of disease, *e.g.* chronic kidney disease, but caution must be exercised given the low MACE events in the UK CF Registry and subsequent lack of discriminatory power. Women are generally considered to be at lower risk for the MACE outcomes used in this study; although we found no evidence of this in the TriNetX cohort, there was a trend towards reduced MACE prevalence in females but this did not reach statistical significance. We did observe sex distribution disparity between TriNetX and the UK CF Registry, and ultimately complete population studies may be needed to address sex differences in CF cardiac outcomes.

Chronic inflammation is a hallmark of CF and has been independently associated with cardiac disease in other conditions. For example, diseases such as SLE and rheumatoid arthritis are associated with increased cardiac disease, in excess of that attributable to classic cardiac risk factors [6–8]. Here, we found that

despite adjusting for the presence of classic cardiac risk factors, risk of cardiac disease in CF was equivalent to or greater than that of other inflammatory conditions. Pulmonary inflammation in CF is often accompanied by exaggerated protease (*e.g.* neutrophil elastase) activity and neutrophil elastase is strongly associated with CF disease severity [26]. Neutrophil elastase also plays a role in the pathogenesis of atherosclerosis and may be an example of a putative unifying mechanism for some of our findings, particularly given myocardial infarction appeared to be the main driver of MACE in PwCF.

In SLE, rheumatoid arthritis and HIV, conventional cardiac risk prediction tools have been found to under-estimate risk [27, 28]. As a consequence, the most widely utilised risk prediction tool in the UK, QRISK (https://qrisk.org), has been updated to include specific adjustments for risk prediction in these diseases. Our results suggest a similar approach may need to be explored for PwCF. Ultimately, prospective longitudinal studies of cardiac health are needed to evaluate risk stratification tools in CF such that holistic risk reduction interventions can be appropriately targeted. Such holistic or integrated care approaches have been advocated for chronic long-term conditions, requiring multidisciplinary input [29, 30]. For example, in atrial fibrillation management, integrated care has been associated with improved clinical outcomes [31, 32], leading to its recommendation in management guidelines [33].

Our findings of excess risk despite adjustments for classic cardiac risk factors imply some CF-specific factors may play a role in cardiac disease in CF. We found evidence to support this in that lung function and total antibiotic days (markers of disease severity) were both worse in those PwCF and MACE. Other possible disease-specific factors include a direct influence of CFTR in the endothelium, CF-related diabetes effects on myocardial contractility and excess reactive oxygen species. All warrant further investigation given they are potentially modifiable [34–36]. Similarly, all may be modified by highly effective CFTR modulator therapy, and a key avenue of future research is understanding the drivers of cardiac risk in PwCF and the net effect of the complex interplay between the improved CF-specific disease markers and increased exposures to cardiac risk factors as survival increases.

Limitations to this study include the lack of independent adjudication of MACE outcomes and the retrospective nature of the studies. UK CF Registry data are well validated for key CF outcomes; however, the data completeness, quality or standardisation for rarer events, *e.g.* chronic kidney disease and cardiac disease, is not known and under-reporting may explain some differences in incidence between datasets. Similarly, the study cohort may have had MACE events outside of the TriNetX network which would not be captured. TriNetX is a predominantly North American dataset and disparities between healthcare systems may also limit the generalisability of results. Similarly, TriNetX relies on real-time data collection from healthcare organisations' electronic healthcare records and some conditions or outcomes may also be under-reported/misclassified and aggregates can vary slightly over time. Due to limitations of data availability, we are unable to compare the risk of MACE between PwCF in the UK CF Registry and the general population in the UK. In the latter, the QResearch database (www.qresearch.org) suggests a crude incidence for cardiovascular disease of ∼1.4–2.8 per 1000 person-years for ages 35–44 years (the lowest reported age group). The average age in the UK CF Registry population was lower, yet the crude rate here was higher, ∼3.2 per 1000 person-years [37]. Importantly, QResearch uses a much broader definition of cardiovascular disease, including non-acute events, *e.g.* stable angina, perhaps artificially narrowing the difference, but supporting our findings of the increased cardiovascular disease risk in PwCF. We included 2016–2020 data as the most up-to-date data available from the UK CF Registry, but this also includes data captured during the coronavirus disease 2019 pandemic, which had impacts on wider healthcare utilisation and cardiac disease diagnoses which may act as a potential confounder. ICD code disease classification can vary by condition and demographics, and limitations to using solely ICD codes for identification of CF have previously been reported. We minimised this by more strictly defining our CF cohort such that the cohort more appropriately resembled well-validated CF populations. Furthermore, consistent findings across two datasets, including the non-ICD-code-dependent UK CF Registry, helps to reinforce the validity of our findings. We tried to minimise variation in outcome classification by standardising outcomes to those clearly reported/defined in all cohorts, but residual bias may still exist. For example, we have limited data on key cardiac risk factors such as physical activity which may differ between groups or populations. The cohorts are also inherently heterogenous in terms of patient inclusion and direct comparisons between healthcare systems/nations are therefore not possible. Instead, the datasets included in this study collectively provide insight into cardiac disease in CF from a spectrum of healthcare settings and serve as a useful benchmark in the understanding and estimation of cardiac disease risk in CF.

In conclusion, we found PwCF have increased risk of MACE. Prospective studies are needed to confirm these findings, define the determinants of cardiac risk in the CFTR modulator era and assess the validity of cardiac risk prediction tools in the CF setting.

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