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

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Abstract

Introduction:

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 cystic fibrosis.

Methods:

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

Results:

PwCF had high prevalence of diabetes but low rates of hypertension and obesity. Some cardiac risk factors (age, diabetes, hypertension) were associated with MACE, but relationships between disease specific risk factors (lung function and intravenous antibiotic days) were also observed.

In propensity-matched analyses, PwCF had higher risk of MACE than matched general population comparators (Hazard Ratio [95% CI] 1.65 [1.40 to 1.95], $p<0.001$), and an equivalent or higher relative risk compared to other inflammatory conditions considered "high-risk" for cardiovascular disease including rheumatoid arthritis (HR 1.21 [1.00 to 1.48], $p<0.001$), systemic lupus erythematosus (RR 0.95 [0.82 to 1.09], $p=0.44$) and human immunodeficiency virus (HR 0.93 [0.82 to 1.06], $p=0.29$)

Conclusion:

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 cystic fibrosis transmembrane conductance regulator protein (CFTR) modulators which effectively restore CFTR function in over 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 [**RA**] and human immunodeficiency virus infection [**HIV]**) to be associated with excess cardiac risk.[6–8]

A low body mass index, 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 have been considered rare. However, in the face of increasing survival, increasing body mass index and increased fat absorption associated with CFTR modulators the long-term risk for people with CF 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 multi-source 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 people with CF, with over 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 includes demographics, International Classification of Diseases 10th Revision (ICD-10) disease codes, procedures (ICD-10 Procedure Coding system), medication details (rxNorm/Veterans affairs National Formularly codes) and laboratory measurements (coded as Logical Observation Identifiers Names and Codes, LOINC). Data regarding lung function and annual antibiotic usage was only available in the UK CF Registry,

Study population:

Adults (>18 years old in 2016) with cystic fibrosis 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, co-morbidities 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 people with CF. Mandating a hospital encounter and ≥4 instances of an ICD-10 code for cystic fibrosis defined a cohort that closely resembled those seen in well-validated sources such as the UK CF Registry and US CFF Registry, see Supplementary Figure S1. Those without any codes for CF were considered the non-CF general population cohort. For comparisons between CF against other inflammatory diseases, individuals with SLE, RA 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 Figure S3. Throughout, clinical

characteristics were recorded at index which was 2016 for UK CF Registry and the hospital encounter in 2016 for TriNetX.

Cardiac outcomes:

Available cardiac outcomes were variable across datasets, see Figure S2. A core outcome set of major adverse cardiac events (**MACE**) including myocardial infarction, left sided heart failure and atrial fibrillation (**AF**) 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 available 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 30th April 2023. Throughout, univariate analyses consisted of Chi-squared tests for categorical and independent sample t-tests for continuous variables. Missing data was only observed for LOINC variables e.g. body mass index (19.8% missing). Given these values were only used in descriptive context no imputations for missing data were performed. In the TriNetX platform, comparisons were made between PwCF against general population, and active disease controls (HIV, RA, SLE). Standardized mean differences (Std diff.) 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 standardized differences for that variable. Propensity score matching (PSM) consisting of a 1:1 matching by logistic regression. A greedy nearest neighbour matching algorithm with and 0.1 pooled standard deviations of the propensity scores in aggregate wasused 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 Std diff.<0.100 was considered well matched and details are provided in

Supplementary section E3. After PSM, Cox's proportional hazard model was use to compared the matched cohorts.

Results

Data were available for 5649 adult PwCF In the UK CF Registry, mean (SD) age 32.2 (11) years, and 6265 adult PwCF in TriNetX, mean (SD) age 27.8. (10) 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, average BMI was 23.1 kg/m^2 and 24.4 kg/m^2 respectively, but a lower prevalence of hypertension in the UK CF Registry (2.2% versus 11.8%) was observed. There were more females in TriNetX, (64% versus 45% in UK CF Registry). Prevalence of diabetes was variable: present in 35% 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 433/6265 (6.9%). In the same study period, MACE was recorded for 89/5649 (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 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 to 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 people with CF

(Hazard Ratio [95% Confidence Interval] 1.75 [1.59 to 1.92], p<0.001), see Table 3. After successful propensity score matching of all 6265 PwC, the increased risk of MACE remained (HR 1.65 [1.40 to 1.95], p<0.001) and was driven largely by myocardial infarction (HR [95% CI] 2.13 [1.66 to 2.73]), see Figure 2. This finding was consistent across unmatched analyses and also when only matched for age and sex, see Table 3 & 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, see Table S8 & S9.

Outcomes compared to 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 37098, 97198 and 91699 people living with SLE, RA and HIV respectively with those from the general population, see Table E2.2-2.4. All three were associated with increased MACE, see Supplementary Analyses 2-4. 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, RA and HIV comparators respectively), see Table 4. In CF, risk of MACE was equivalent to SLE and HIV (Hazard Ratio [95% CI] 0.95 [0.82 to 1.09], *p*=0.44 and Hazard Ratio [95% CI] 0.93 [0.82 to 1.06],*p*=0.29) respectively, and was greater than RA (HR [95% CI] 1.21 [1.00 to 1.48]), see Table S2, S4 & S6 for composite breakdown.

Discussion:

We used two independent datasets to investigate cardiac disease in CF. Our main findings are that people living with CF have a significantly higher risk of cardiac disease than matched counterparts in the general population. Furthermore, cardiac risk in PwCF was equivalent or higher to 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 cystic fibrosis, and more recently pre-lung transplant angiograms were reported to be normal in 14 adults with CF.[14,15] However, these findings are unlikely to be generalisable to an increasingly older co-morbid 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 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 people living with CF has progressively improved over recent decades with current median life-expectancy of 53.3 years in the UK.[19] In the last few years highly effective disease modifying drugs, CFTR modulators, have become available and are likely to herald an even greater increase in life expectancy. However, increasing age, body mass index and high-prevalence of cystic fibrosis related diabetes have generated concerns that people living with CF may become high-risk for cardiac diseases. The results from this study, conducted across two datasets before widespread availability of CFTR modulators, suggest annualised MACE incidence ranges 0.3-1.3%. Importantly, our findings demonstrated that people with CF 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 people with CF 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 approximately ~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 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 cystic fibrosis related diabetes. Diabetesprevalence appeared variable between datasets with over 35% prevalence in the UK CF Registry but 26% in the TriNetX data. Given the poor prognostic outcomes of CFRD, 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, CFRD 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 diagnosis of CFRD may also be a contributory factor.[25] Differences were also observed between groups where those with MACE had 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, and 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 cystic fibrosis and has been independently associated with cardiac disease in other conditions. For example, diseases such as SLE and RA 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 or greater to 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, HIV and RA, 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, 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 AF 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 factor 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, CFRD 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

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 like 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 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 suggests a crude incidence for cardiovascular disease of approximately 1.4 to 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 crude rate here was higher, approximately 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 CVD risk in pwCF. We included data 2016-2020 as the most up to date data available from the UK CF Registry, but this also includes data captured during the COVID-19 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 be 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 people living with CF have increased risk of major adverse cardiac events. 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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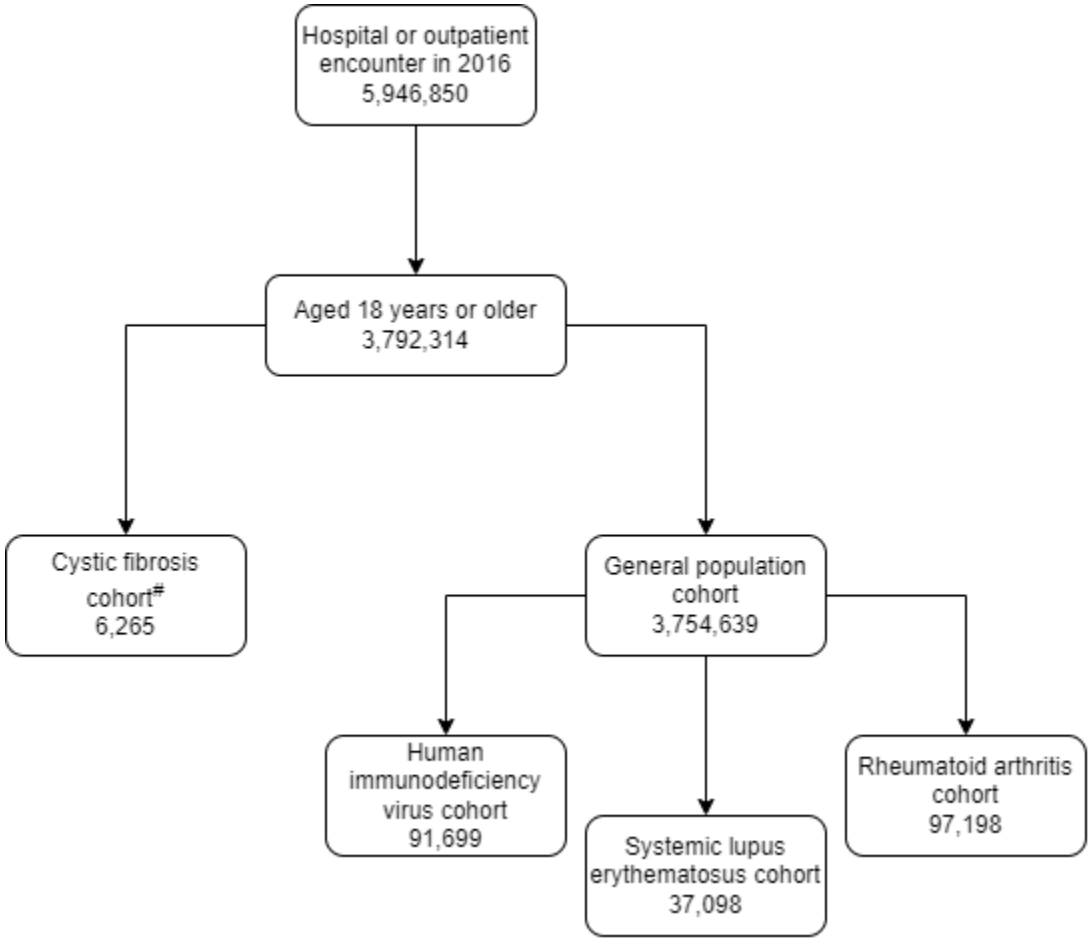
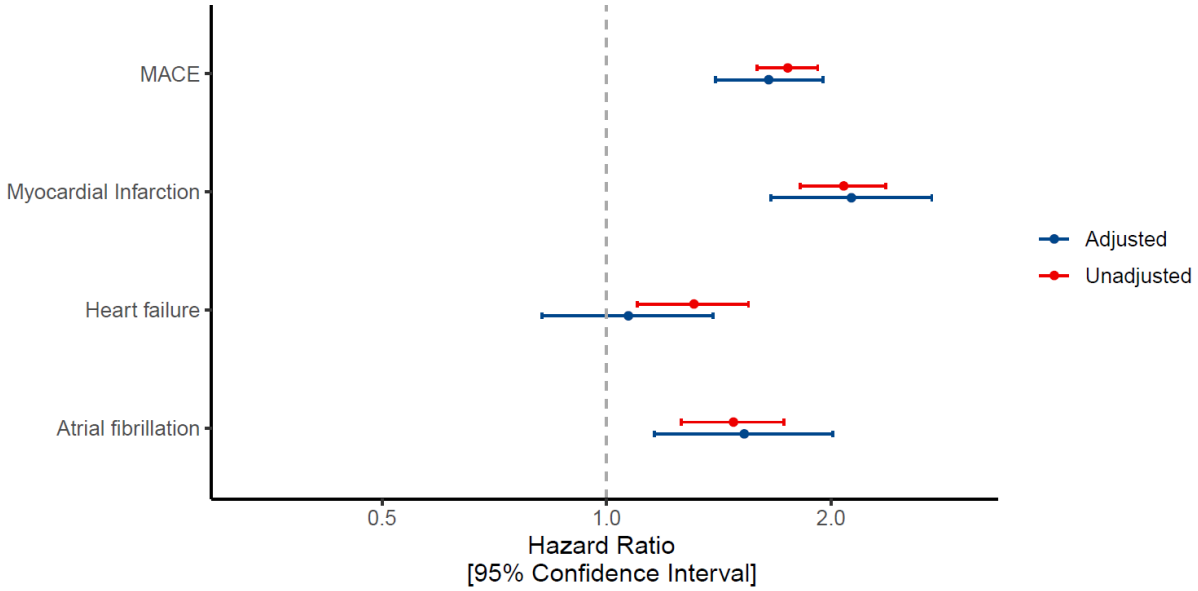
Figure 1: Cohort identification within the TriNetX Dataset



#Cystic fibrosis cohort defined by 4 or more instances of ICD-10 code E84

Figure 2: Hazard ratio and 95% confidence intervals for risk of major adverse cardiac events in people living with cystic fibrosis versus general population comparators in unadjusted and adjusted[#] analyses. Analyses conducted in TriNetX population only.



Abbreviations: MACE=Major adverse cardiac event

#=Adjusted analyses were propensity score matched for cardiac risk factors (diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease)

Table 1: Baseline clinical characteristics of adults living with cystic fibrosis in the UK Cystic Fibrosis Registry and TriNetX datasets.

	UK CF Registry	**TriNetX**
	N=5649	N=6265
Age, *mean (SD)*	32.1 (11.0)	27.8 (10.1)
Sex, *female* %	2549 (45.1%)	3981 (63.5%)
Body Mass Index (kg/m2), *mean (SD)*	23.1 (4.2)	24.4 (6.4)
Hypertension, %	127 (2.2%)	743 (11.8%)
Hypercholesterolaemia, %	N/A	65 (1.0%)
Obesity (BMI>30kg/m2), %	309 (5.5%)	338 (5.4%)
Family history of Ischaemic heart disease, %	N/A	195 (3.1%)
Smoking, %	N/A	126 (2.0%)
Diabetes, %	1996 (35.3%)	1675 (26.7%)
Chronic Kidney Disease, %	88 (1.6%)	333 (5.3%)

Abbreviations: BMI=Body Mass Index

Table 2: Characteristics of people living with cystic fibrosis with comparison by major adverse cardiac events in the UK CF Registry (2A) and TriNetX (2B)

Table 2A	No MACE	MACE	p
n	5560	89	
Age, mean (SD	31.9 (10.8)	46.4 (14.7)	<0.001
Sex, female (%)	2518 (45.3)	31 (34.8)	0.063
Body mass index, kg/m2, mean (SD))	23.1 (4.2)	23.7 (4.1)	0.195
Obese (%)	303 (5.4)	6 (6.7)	0.777
Cystic Fibrosis 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
FEV1, % predicted, mean (SD))	63.3 (14.7)	54.4 (23.6)	<0.001
P. aeruginosa (%)	3155 (56.7)	56 (62.9)	0.422
Intravenous antibiotic days, mean (SD)	19.8 (32.7)	38.3 (51.7)	<0.001

Table 2B	**No MACE**	**MACE**	***p***
n	**5832**	**433**	
Age, mean (SD))	**27.5 (10.2)**	**33.2 (10.1)**	***<0.001***
Sex, female (%)	**3693 (67.9)**	**288(66.5)**	***0.50***
Body mass index, mean (SD))	**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***

Abbreviations: CF=Cystic Fibrosis;MACE=Major adverse cardiac events; FEV1: Forced expiratory volume in 1 second; IV=intravenous antibiotic

Table 3: Comparison of risk for cardiac disease between people with cystic fibrosis and the general population. Propensity score matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease). Analyses conducted in TriNetX population only.

	Unadjusted Analysis								Propensity Score Matched Analysis							
	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p
MACE	6,265	433	3,754,639	121,921	1.75	1.59	1.92	<0.001	6,265	433	6,265	215	1.65	1.40	1.95	<0.001
Myocardial infarction	6,265	227	3,754,639	52,566	2.08	1.82	2.37	<0.001	6,265	227	6,265	86	2.13	1.66	2.73	<0.001
Heart failure	6,265	129	3,754,639	48,144	1.31	1.10	1.55	<0.001	6,265	129	6,265	98	1.07	0.82	1.39	0.65
Atrial fibrillation	6,265	148	3,754,639	49,233	1.48	1.26	1.73	<0.001	6,265	148	6,265	79	1.53	1.16	2.01	0.002

Abbreviations: CI=confidence interval; CF=cystic fibrosis; MACE=major adverse cardiovascular event (composite of myocardial infarction, left-sided heart failure and atrial fibrillation);

Table 4: Comparison of risk for major adverse cardiac events between people with cystic fibrosis and other inflammatory conditions. 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).

	Unadjusted Analysis								Propensity Score Matched Analysis							
	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p
SLE	6,265	433	37,098	3,984	0.61	0.56	0.68	<0.001	5,223	385	5,223	389	0.95	0.82	1.09	0.439
Rheumatoid arthritis	6,265	227	97,198	4,547	0.75	0.66	0.86	<0.001	5,901	223	5,901	177	1.21	1.00	1.48	0.055
HIV	6,265	433	91,699	9,173	0.67	0.61	0.74	<0.001	6,192	430	6,192	461	0.93	0.82	1.06	0.293

Abbreviations: CI=confidence interval; CF=cystic fibrosis; MACE=major adverse cardiovascular event (composite of myocardial infarction, left-sided heart failure and atrial fibrillation); SLE=Systemic Lupus Erythematosous;RA=Rheumatoid Arthritis;HIV = Human immunodeficiency virus

Supplementary File

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

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Derivation and optimisation of cystic fibrosis cohort in TriNetX

Given, the validity and generalisability of ICD-10 code based research in CF is unclear, we sought to optimise a CF cohort definition within TriNetX. Rather than simply rely on an isolated ICD-10 code alone we combined hospital encounters and frequency of CF ICD-10 codes into a cohort definition to more precisely identify people with CF. We found mandating a hospital encounter and >4 instances of an ICD-10 code for cystic fibrosis reduced the potential cohort down from ~30000 patients to ~6000 but improved the cohort characteristics to more closely resemble those seen in well-validated sources such at the UK CF Registry and US CFF Registry, see Figure S1.

Figure S1: Comparison of characteristics between CF population in TriNetX using ICD-10 code alone, optimised method (combination of hospital encounter in 2020 and multiple instances of ICD-10 code), US CFF Registry Report 2020, UK CF Registry Report 2020

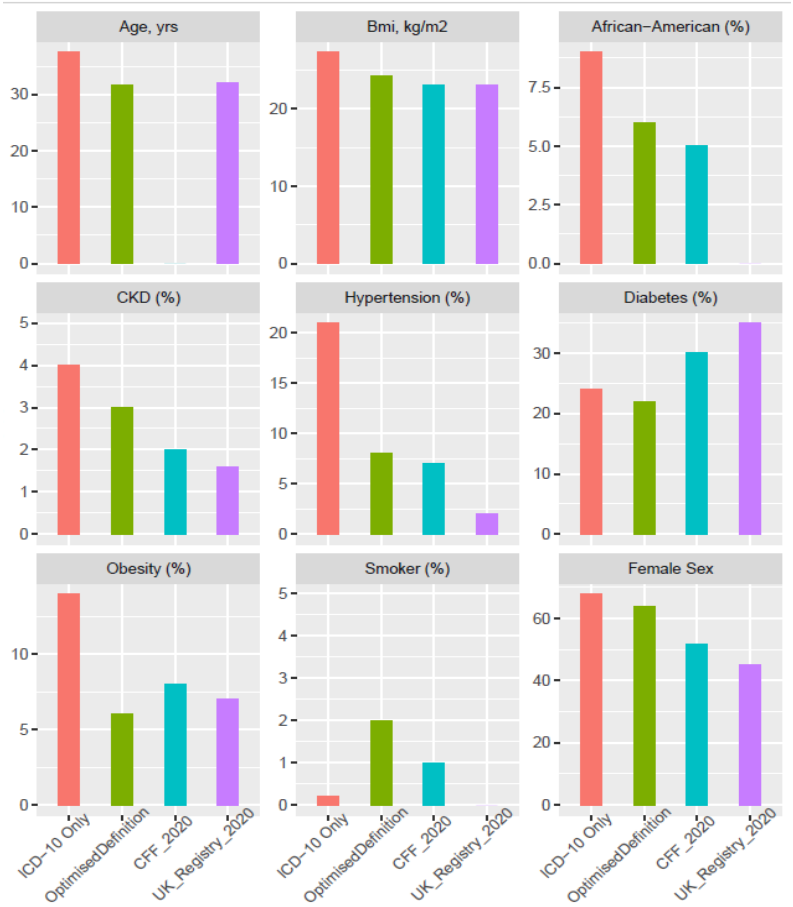

Figure S2: Data Map indicating availability (green) or unavailability (red) of data points across the two data sets

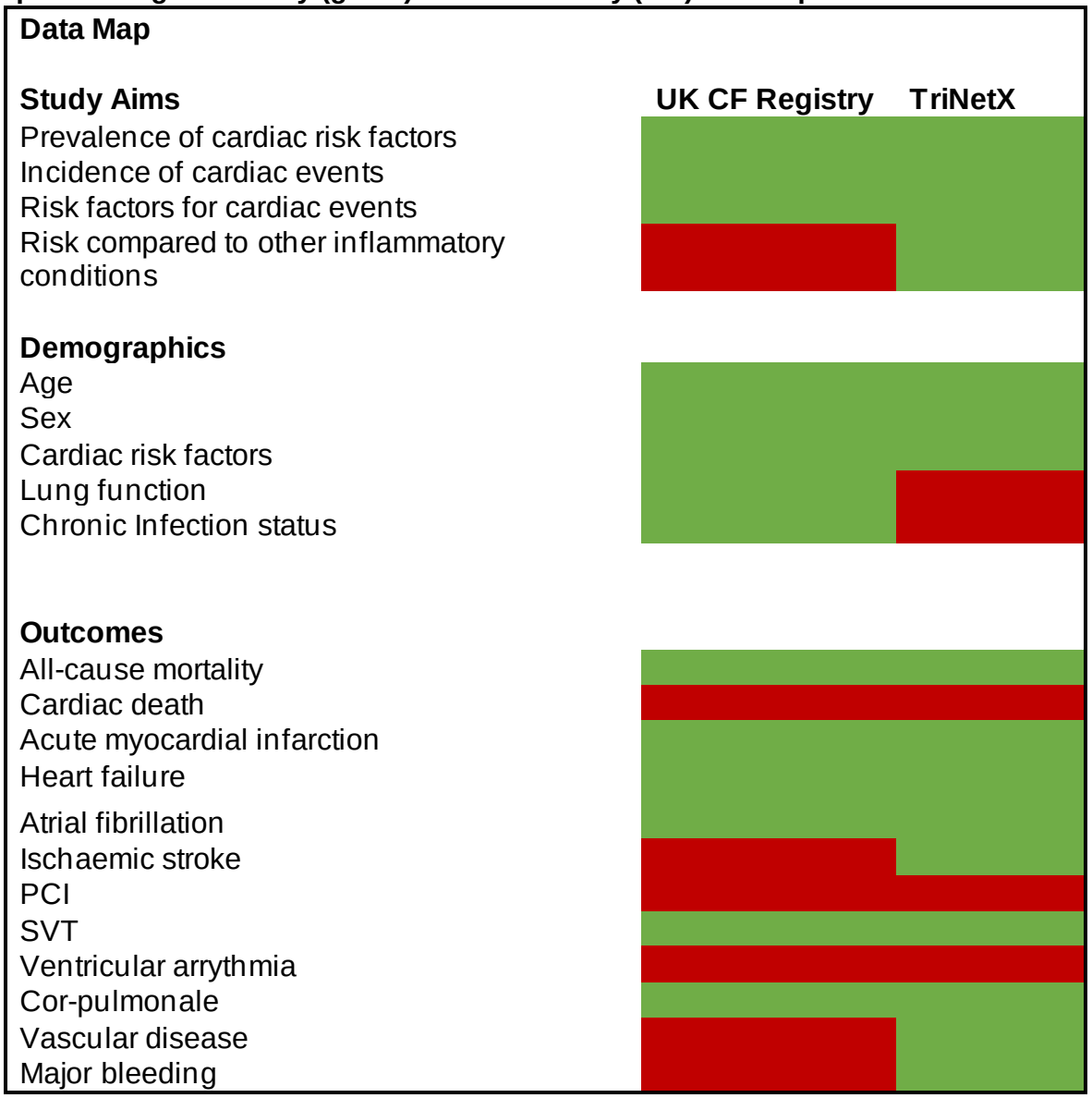

Figure S3: Diagram describing how all groups (including subgroups) were cohorted within TrinetX

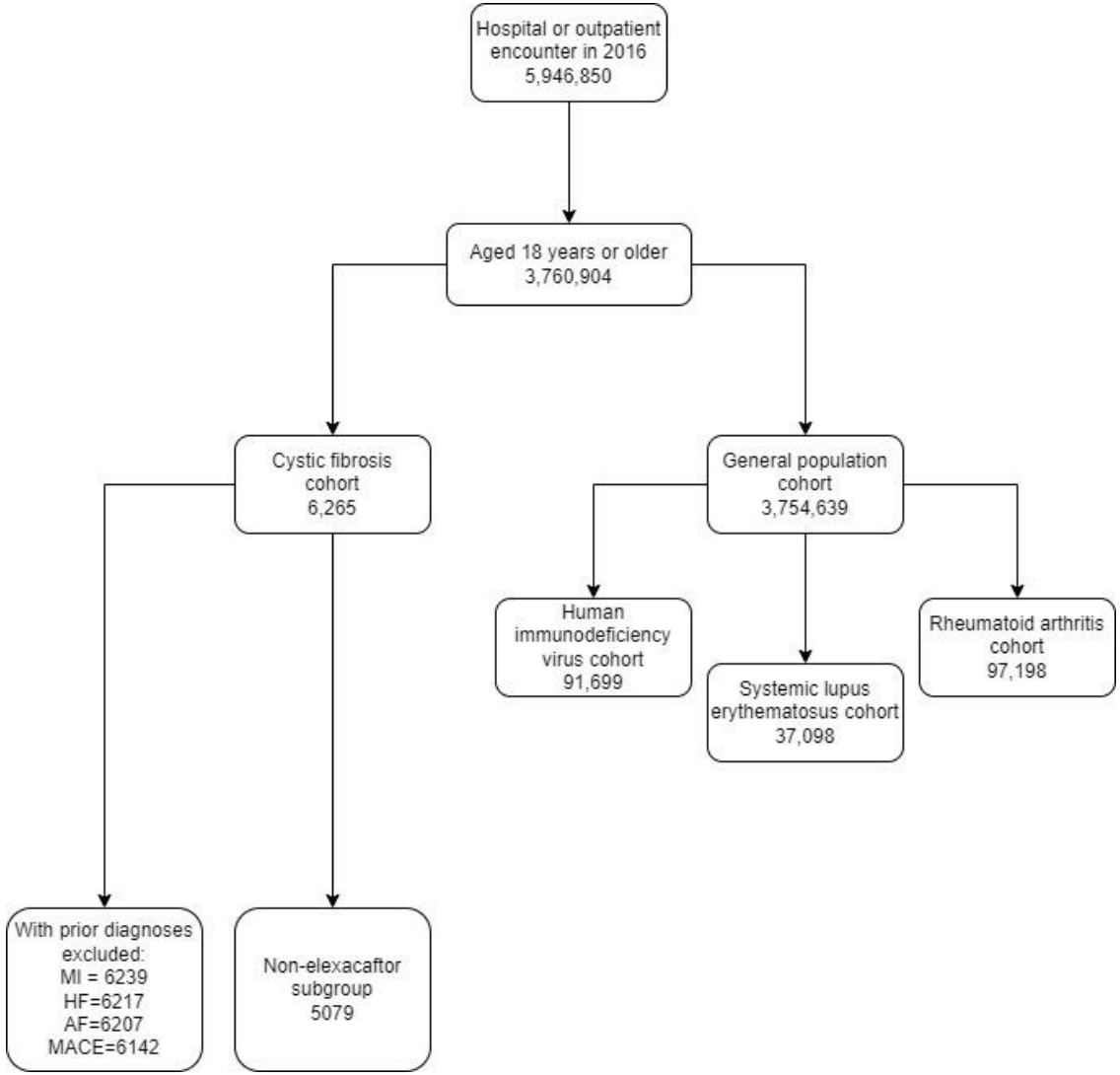

Table E1: Inclusion Criteria For Each Group

Group	Inclusion Criteria
Cystic fibrosis	Age>18 Must have ICD-10 E84 x 4 Hospital inpatient or outpatient visit in 1/1/2016 to 1/1/2017
General population	Age>18 Cannot have E84 Hospital inpatient or outpatient visit in 1/1/2016 to 1/1/2017
Systemic Lupus Erythematosous	Age>18 Cannot have E84 Hospital inpatient or outpatient visit in 1/1/2016 to 1/1/2017 Must have ICD-10 M32
Rheumatoid Arthritis	Age>18 Cannot have E84 Hospital inpatient or outpatient visit in 1/1/2016 to 1/1/2017 Must have M06.9 or M06
HIV	Age>18 Cannot have E84 Hospital inpatient or outpatient visit in 1/1/2016 to 1/1/2017 Must Have Z21 or B20

Table E2:Outcome ICD-10 Codes

Outcome	**ICD-10 Code**
Myocardial Infarction	I21 Myocardial infarction
Heart failure	I50.1 (Left Ventricular failure) OR I50.2 (Systolic congestive heart failure) OR I50.3 (Diastolic congestive heart failure)
Atrial fibrillation	I48 Atrial fibrillation and flutter
MACE-AF	composite of the above (I21 or I50.1 or I50.2 or I50.3 or I48)

Section E3: Results of Propensity Score Matching

Table E3.1: Cystic fibrosis vs General population. Analyses conducted in TriNetX population only.

		Before PSM						After PSM					
Baseline Patient Characteristics		**CF**		**Gen Popln**				**CF**		**Gen Popln**			
	Characteristic Name	n	%	n	%	p	SMD	n	%	n	%	p	SMD
E08-E13	Diabetes mellitus	1736	27.71%	240487	6.41%	0.000	0.591	1732	27.66%	1739	27.78%	0.889	0.002
I10	Essential (primary) hypertension	743	11.86%	493622	13.15%	0.003	0.039	741	11.84%	730	11.66%	0.760	0.005
N18	Chronic kidney disease (CKD)	333	5.32%	116295	3.10%	0.000	0.111	331	5.29%	323	5.16%	0.748	0.006
F17.200	Nicotine dependence, unspecified, uncomplicated	281	4.49%	256629	6.84%	0.000	0.102	281	4.49%	288	4.60%	0.764	0.005
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system	195	3.11%	71444	1.90%	0.000	0.077	193	3.08%	194	3.10%	0.959	0.001
Z72.0	Tobacco use	126	2.01%	97421	2.60%	0.004	0.039	126	2.01%	136	2.17%	0.532	0.011
E78.0	Pure hypercholesterolemia	65	1.04%	90035	2.40%	0.000	0.105	65	1.04%	62	0.99%	0.789	0.005

Abbreviation: PSM=Propensity Score Matching; SMD=Standardised Mean Differences;

Table E3.2: Cystic fibrosis vs Systemic Lupus Erythematosus. Analyses conducted in TriNetX population only.

		Before PSM						After PSM					
		CF			**SLE**			**CF**			**SLE**		
Characteristic ID	Characteristic Name	n	%	n	%	p	SMD	n	%	n	%	p	SMD
E08-E13	Diabetes mellitus	1736	27.71%	3966	10.69%	0.000	0.443	1046	20.03%	920	17.61%	0.002	0.062
I10	Essential (primary) hypertension	743	11.86%	10671	28.76%	0.000	0.430	705	13.50%	649	12.43%	0.103	0.032
N18	Chronic kidney disease (CKD)	333	5.32%	4611	12.43%	0.000	0.252	318	6.09%	281	5.38%	0.119	0.030
F17.200	Nicotine dependence, unspecified, uncomplicated	281	4.49%	4270	11.51%	0.000	0.261	265	5.07%	277	5.30%	0.597	0.010
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system	195	3.11%	1422	3.83%	0.005	0.039	161	3.08%	151	2.89%	0.565	0.011
Z72.0	Tobacco use	126	2.01%	1517	4.09%	0.000	0.121	116	2.22%	130	2.49%	0.366	0.018
E78.0	Pure hypercholesterolemia	65	1.04%	1309	3.53%	0.000	0.167	64	1.23%	65	1.24%	0.929	0.002

Abbreviation: PSM=Propensity Score Matching; SMD=Standardised Mean Differences;SLE=Systemic Lupus Eythematosous

Table E3.3: Cystic fibrosis vs Rheumatoid Arthritis. Analyses conducted in TriNetX population only.

		Before PSM						After PSM					
Baseline Patient Characteristics		**CF**			**RA**			**CF**			**RA**		
Characteristic ID	Characteristic Name	n	%	n	%	p	SMD	n	%	n	%	p	SMD
E08-E13	Diabetes mellitus	1736	27.71	13185	13.57%	0.000	0.355	1372	23.25%	1342	22.74%	0.512	0.012
I10	Essential (primary) hypertension	743	11.86%	25098	25.82%	0.000	0.363	729	12.35%	699	11.85%	0.397	0.016
N18	Chronic kidney disease (CKD)	333	5.32%	9870	10.16%	0.000	0.182	326	5.52%	339	5.75%	0.604	0.010
F17.200	Nicotine dependence, unspecified, uncomplicated	281	4.49%	12863	13.23%	0.000	0.312	277	4.69%	292	4.95%	0.519	0.012
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system	195	3.11%	2958	3.04%	0.757	0.004	177	3.00%	169	2.86%	0.662	0.008
Z72.0	Tobacco use	126	2.01%	5428	5.58%	0.000	0.188	122	2.07%	138	2.34%	0.316	0.018
E78.0	Pure hypercholesterolemia	65	1.04%	6250	6.43%	0.000	0.287	65	1.10%	65	1.10%	1.000	0.000

Abbreviation: PSM=Propensity Score Matching; SMD=Standardised Mean Differences; RA=Rheumatoid arthritis

Table E3.4: Cystic fibrosis vs HIV. Analyses conducted in TriNetX population only.

		Before PSM						After PSM					
Baseline Patient Characteristics		**CF**		**HIV**				**CF**		**HIV**			
Characteristic ID	Characteristic Name	n	%	n	%	p	SMD	n	%	n	%	p	SMD
E08-E13	Diabetes mellitus	1736	27.71	8640	9.42%	0.000	0.368	1351	21.82 %	1349	21.79 %	0.965	0.001
I10	Essential (primary) hypertension	743	11.86%	16370	17.85%	0.000	0.296	503	8.12%	500	8.08%	0.921	0.002
N18	Chronic kidney disease (CKD)	333	5.32%	10332	11.27%	0.000	0.274	253	4.09%	250	4.04%	0.891	0.002
F17.200	Nicotine dependence, unspecified, uncomplicated	281	4.49%	8559	9.33%	0.000	0.326	120	1.94%	118	1.91%	0.896	0.002
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system	195	3.11%	6337	6.91%	0.000	0.281	86	1.39%	93	1.50%	0.598	0.009
Z72.0	Tobacco use	126	2.01%	1567	1.71%	0.006	0.038	78	1.26%	72	1.16%	0.622	0.009
E78.0	Pure hypercholesterolemia	65	1.04%	2121	2.31%	0.000	0.157	30	0.48%	26	0.42%	0.592	0.010

Abbreviation: PSM=Propensity Score Matching; SMD=Standardised Mean Differences; HIV=Human immunodeficiency virus

Supplementary Analysis 1: CF vs General Population (adjusted for Age and Sex Only). Analyses conducted in TriNetX population only.

Table S1: Comparison of risk for cardiac disease between people with cystic fibrosis (CF) and the general population. Propensity matching based on age and sex only.

	Unadjusted Analysis								Propensity Matched Analysis							
	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p
MACE	6,265	433	3,754,639	121,921	1.75	1.59	1.92	<0.001	6,265	433	6,265	150	2.32	1.92	2.79	<0.001
Myocardial infarction	6,265	227	3,754,639	52,566	2.08	1.82	2.37	<0.001	6,265	227	6,265	70	2.55	1.95	3.34	<0.001
Heart failure	6,265	129	3,754,639	48,144	1.31	1.10	1.55	<0.001	6,265	129	6,265	56	1.82	1.33	2.48	<0.001
Atrial fibrillation	6,265	148	3,754,639	49,233	1.48	1.26	1.73	<0.001	6,265	148	6,265	56	2.10	1.54	2.85	<0.001

Supplementary Analysis 2: Comparison with systemic lupus erythematosus (ICD-10 M32). Analyses conducted in TriNetX population only.

Table S2: Comparison of risk for cardiac disease between SLE and cystic fibrosis. Propensity matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Matched Analysis							
	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p
MACE	6,265	433	37,098	3,984	0.61	0.56	0.68	<0.001	5,223	385	5,223	389	0.95	0.82	1.09	0.439
Myocardial infarction	6,265	227	37,098	1,775	0.73	0.64	0.84	<0.001	5,223	215	5,223	175	1.18	0.97	1.44	0.108
Heart failure	6,265	129	37,098	1,991	0.37	0.31	0.44	<0.001	5,223	113	5,223	162	0.66	0.52	0.84	0.001
Atrial fibrillation	6,265	148	37,098	1,379	0.62	0.52	0.73	<0.001	5,223	121	5,223	129	0.90	0.70	1.15	0.387

Table S3: Comparison of risk for cardiac disease between SLE and general population. Propensity matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Matched Analysis							
	SLE	Events	Non-SLE	Events	Hazard Ratio	95% CI		p	SLE	Events	Non-SLE	Events	Hazard Ratio	95% CI		p
MACE	37,098	3,985	3,754,639	121,921	2.85	2.76	2.94	<0.001	37,098	3,985	37,098	2,439	1.48	1.41	1.56	<0.001
Myocardial infarction	37,098	1,775	3,754,639	52,566	2.83	2.70	2.97	<0.001	37,098	1,775	37,098	1,041	1.52	1.40	1.64	<0.001
Heart failure	37,098	1,991	3,754,639	48,144	3.56	3.40	3.72	<0.001	37,098	1,991	37,098	1,234	1.46	1.36	1.56	<0.001
Atrial fibrillation	37,098	1,380	3,754,639	49,233	2.40	2.27	2.53	<0.001	37,098	1,380	37,098	878	1.41	1.30	1.54	<0.001

Supplementary Analysis 3: Comparison with rheumatoid arthritis (ICD-10 M06.9 or M06). Analyses conducted in TriNetX population only.

Table S4: Comparison of risk for cardiac disease between rheumatoid arthritis and cystic fibrosis. Propensity matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Score Matched Analysis							
	CF	Events	RA	Events	Hazard Ratio	95% CI		p	CF	Events	RA	Events	Hazard Ratio	95% CI		p
MACE	6,265	227	97,198	4,547	0.75	0.66	0.86	<0.001	5,901	223	5,901	177	1.21	1.00	1.48	0.055
Myocardial infarction	6,265	129	97,198	3,391	0.57	0.48	0.68	<0.001	5,901	123	5,901	122	0.97	0.75	1.24	0.792
Heart failure	6,265	148	97,198	3,163	0.71	0.60	0.83	<0.001	5,901	142	5,901	116	1.18	0.92	1.51	0.185
Atrial fibrillation	6,265	433	97,198	8,393	0.73	0.66	0.81	<0.001	5,901	397	5,901	327	1.17	1.01	1.36	0.03

Table S5: Comparison of risk for cardiac disease between rheumatoid arthritis and general population. Propensity matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								PropensityScore Matched Analysis							
	RA	Events	Gen. popln	Events	Hazard Ratio	95% CI		p	RA	Events	Non-RA	Events	Hazard Ratio	95% CI		p
MACE	97,198	8,772	3,754,639	121,921	2.37	2.32	2.42	<0.001	97,198	8,772	97,198	6,022	1.30	1.26	1.35	<0.001
Myocardial infarction	97,198	4,547	3,754,639	52,566	2.76	2.68	2.85	<0.001	97,198	4,547	97,198	2,829	1.42	1.35	1.49	<0.001
Heart failure	97,198	3,391	3,754,639	48,144	2.29	2.21	2.37	<0.001	97,198	3,391	97,198	2,656	1.14	1.08	1.19	<0.001
Atrial fibrillation	97,198	3,163	3,754,639	49,233	2.09	2.02	2.17	<0.001	97,198	3,163	97,198	2,274	1.24	1.18	1.31	<0.001

Supplementary Analysis 4: Comparison with human immunodeficiency virus (ICD-10 B20 or Z21). Analyses conducted in TriNetX population only.

Table S6: Comparison of risk for cardiac disease between human immunodeficiency virus infection and cystic fibrosis. Propensity matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Score Matched Analysis							
	CF	Events	HIV	Events	Hazard Ratio	95% CI		p	CF	Events	HIV	Events	Hazard Ratio	95% CI		p
MACE	6,265	433	91,699	9,173	0.67	0.61	0.74	<0.001	6,192	430	6,192	461	0.93	0.82	1.06	0.293
Myocardial infarction	6,265	227	91,699	6,140	0.53	0.46	0.60	<0.001	6,192	225	6,192	330	0.68	0.57	0.80	<0.001
Heart failure	6,265	129	91,699	2,988	0.62	0.52	0.74	<0.001	6,192	128	6,192	116	1.10	0.86	1.42	0.449
Atrial fibrillation	6,265	148	91,699	2,419	0.88	0.75	1.04	0.144	6,192	147	6,192	92	1.60	1.23	2.07	<0.001

Table S7: Comparison of risk for cardiac disease between HIV and general population. Propensity matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Score Matched Analysis							
	HIV	Events	Gen. popln	Events	Hazard Ratio	95% CI		p	HIV	Events	Non-RA	Events	Hazard Ratio	95% CI		p
MACE	91,699	9,173	3,754,639	121,921	2.59	2.54	2.65	<0.001	91,699	9,173	91,699	5,374	1.45	1.41	1.50	<0.001
Myocardial infarction	91,699	6,140	3,754,639	52,566	3.93	3.83	4.03	<0.001	91,699	6,140	91,699	2,808	1.84	1.76	1.92	<0.001
Heart failure	91,699	2,988	3,754,639	48,144	2.10	2.03	2.18	<0.001	91,699	2,988	91,699	2,201	1.15	1.09	1.22	0.005
Atrial fibrillation	91,699	2,419	3,754,639	49,233	1.67	1.60	1.74	<0.001	91,699	2,419	91,699	1,884	1.09	1.03	1.16	0.01

Supplementary Analysis 5: Sensitivity analysis exploring the influence of prior diagnoses of cardiac disease to outcomes of our primary analysis. Analyses conducted in TriNetX population only.

Table S8: Comparison of risk for cardiac disease between people with cystic fibrosis (CF) and the general population between the primary analysis and a restriction analysis (restricted to those without any prior history of outcomes). Propensity score matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Score Matched Analysis							
	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p
Primary analysis	**6,265**	433	3,754,639	121,921	1.75	1.59	1.92	<0.001	6,265	433	6,265	215	1.65	1.40	1.95	<0.001
Restricted analysis	6,142	369	3,688,660	83,393	2.13	1.93	2.36	<0.001	6,142	369	6,207	115	2.55	2.07	3.15	<0.001

Supplementary Analysis 6: Sensitivity analysis exploring the influence of elexacaftor/tezacaftor/ivacaftor use during the study period. Analyses conducted in TriNetX population only.

Table S9: Comparison of risk for major adverse cardiac event between people with cystic fibrosis (CF) and the general population between the primary analysis and a restriction analysis (restricted to those with no use of elexacaftor/tezacaftor/ivacaftor during the study period). Propensity score matching based on known cardiac risk factors (age, sex, diabetes, hypertension, hypercholesterolaemia, family history of heart disease, smoking and chronic kidney disease).

	Unadjusted Analysis								Propensity Score Matched Analysis							
	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p	CF	Events	Non-CF	Events	Hazard Ratio	95% CI		p
Primary analysis	6,265	433	3,754,639	121,921	1.75	1.59	1.92	<0.001	6,265	433	6,265	215	1.65	1.40	1.95	<0.001
Restriction analysis	5,079	384	3,754,639	121,921	1.96	1.77	2.17	<0.001	5,079	384	5,079	132	2.39	1.97	2.92	<0.001