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Risk of SARS-CoV-2 infection and disease severity among people with bronchiectasis; analysis of three population registries.

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Keywords: Bronchiectasis; COVID19; population registry; SARS-CoV-2 infection

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Keywords: Bronchiectasis; COVID19; population registry; SARS-CoV-2 infection

COVID-19 impact on people with airway disease is inconsistent, with different effects on cystic fibrosis(1), COPD(2), and asthma. A collaboration between researchers and patients identified questions related to COVID-19 and chronic airways conditions. Among these were severity of COVID-19 in people with lung disease and the additional risk of treatment with inhaled corticosteroids (ICS) if infected with SARS-COV2(3).

Using population registries, we conducted a retrospective cohort study aiming to assess: 1. The risk of individuals with bronchiectasis of becoming infected with SARS-CoV-2 and: 2. The risk of an adverse outcome if infected. In December 2020, we invited all centers in EMBARC (European Multicenter Bronchiectasis Audit and Research Collaboration)(4) to participate, looking for Electronic Medical Registries (EMR) of a national/regional population. Centers with available EMRs were Catalonia (5), Denmark (6), and Israel(7).

To assess the association between bronchiectasis and SARS-CoV-2 infection, we identified in each EMR adults ≥ 18 years as of 01/01/2020 (cohort entry date). People with bronchiectasis were frequency matched by sex, age ±2 years, and region with people without bronchiectasis using ratios of 1:10 (Denmark) 1:9 (Israel) and 1:2 (Catalonia) subjects. Participants were followed from 01/01/2020 until the occurrence of positive SARS-CoV-2 PCR, death, or 12/31/2020, whichever came first.

To assess the association between bronchiectasis and severe COVID-19 or death, we included adults with positive SARS-CoV-2 PCR between 01/01/2020 and 12/31/2020 (prior to COVID-19 vaccination). Matching was performed by sex, age ±2 years, and the month of positive SARS-CoV-2 PCR, using ratios of (1:5) Denmark, 1:9 (Israel) and 1:2 (Catalonia) Patients were followed from the date of positive PCR until the occurrence of the outcome of interest (disease severity or death), maximum 90 days follow-up or end of follow-up: 01/31/2021, whichever came first. COVID-19 severity was determined as per WHO definitions (8).

Variables retrieved from the EMR included age, sex, ethnicity, socioeconomic status (SES) or income in tertile groups, smoking status (ever vs. never), and comorbidities including COPD, asthma, pulmonary fibrosis, obesity, hypertension, diabetes, ischemic heart disease (IHD), stroke, congestive heart failure (CHF), malignancy, renal failure, liver disease, rheumatoid arthritis, systemic corticosteroids (SCS) use in the prior 6 months, and ICS use in the prior 6 months.

Statistical analyses were conducted separately for each of the study cohorts. Baseline characteristics for individuals with bronchiectasis and controls

were compared using the Chi-square test for the categorical variables and the independent t-test for age. For each study, outcome data were analyzed using the Cox regression model, and hazard ratios for COVID-19, COVID-19 severity and mortality were estimated. To account for missing data in the SES, we included the missing data as a separate category in the multivariable model. Hazard ratio estimates, adjusted for all covariates, were combined across studies using random effects meta-analysis model to account for heterogeneity between countries. NCSS 9 2013 (Utah, U.S.A) statistical software was used for the meta analysis. All other analyses were performed using IBM SPSS Statistics 28.0 (IBM, New York, NY). P <.05 for the 2-tailed tests was considered statistically significant.

Data on smoking and obesity were not reliably captured in Denmark, and data on SES were not reliable in the Danish cohort, which used income records as a surrogate for SES. COVID-19 severity (8) was avaliable in the Catalan and Israeli registries. The Danish registry used data on hospitalizations within 30 days of positive PCR as a surrogate for moderate or severe disease. Table 1 describes cohort characteristics.

Objective 1: bronchiectasis and SARS-CoV-2 infection: In multivariate analyses, bronchiectasis was associated with a lower incidence of COVID-19 in the Catalan cohort, but not in the Danish or Israeli cohorts. In the three cohorts, bronchiectasis was not signifcantly associated with COVID-19 infection [pooled HR 0.78 (95% CI, 0.41-1.49)] (Figure 1A).

Objective 2: bronchiectasis and COVID 19 severity: In multivariate analyses, bronchiectasis was associated with a significantly increased risk for severe disease compared to no bronchiectasis in Catalonia and Denmark only; This association was also preserved in the combined analysis (pooled HR 1.43 (1.08-1.90)] (Figure 1B). In the combined analysis, bronchiectasis was not associated with a significant increase in mortality [pooled HR 1.08 (0.90-1.28)] (Figure 1C).

In summary, our analysis shows that bronchiectasis is associated with a slightly but significantly elevated risk for moderate-severe COVID19 , while the risk for mortality does not seem to be altered. Regarding the risk of SARS-CoV-2 infection, the results varied between cohorts, with a significantly lower risk in Catalonia, but not in Israel or Denmark. This discrepancy may reflect different shielding or testing habits of individuals with bronchiectasis. A previous study in general practice clinics in England found that the risk for hospitalization with COVID-19 was significantly elevated in people with

bronchiectasis (HR 1.34, 95% CI (1.20-1.50) after adjustment for demographics and comorbidities). However, the risk of COVID-19 infection was not assessed(9).

Our study confirmed that the risk for severe COVID-19 was slightly but significantly elevated among people with bronchiectasis, but mortality wasn't. We suggest two possible explanations to the difference between the two outcomes: 1. The risk for severe disease is increased, but small in magnitude and is not reflected in mortality, which was a rare event. 2. The definition of severe disease may be subject to misclassification bias, as bronchiectasis may be associated with abnormal chest imaging and desaturation independent of COVID-19 severity, falsely elevating WHO severity scores. The decision to hospitalise may also be influenced from perceived higher risk due to baseline comorbidity.

The main limitation of our study is the possibility of innaccuracy of bronchiectasis diagnosis, and of COVID-19 severity. Furthermore, bronchiectasis severity was not available in our analysis, and may have impacted on COVID19 severity. However, utilizing three cohorts with different local practices, all showing no difference in mortality and only small differences in COVID-19 severity is reassuring to our patients. Our cohorts were very heterogenous in the prevalence of comorbidities among individuals with bronchiectasis. During the study period (2020), vaccinations were not available, and results from studies guiding treatment of hospitalized COVID-19 were not yet published. We may hypothesize that the risk for adverse outcomes from COVID-19 in people with bronchiectasis in subsequent years of the pandemic is even less pronounced.

To conclude, we found that in three countries, a diagnosis of bronchiectasis was associated with a slightly but significantly increased risk of COVID-19 severity, but not with increased mortality.

Table 1: Characteristics of the study cohorts

Variable (No. (%	Catalonia			Denmark			Israel		
	Bronchiectasis N=16647	**Controls N=33294**	**p-value**	**Bronchiectasis N=14484**	**Controls N=144840**	**p-value**	**Bronchiectasis N=9978**	**Controls N=89802**	**p-value**
Age (years)	80.4±8.8	80.6±8.6	<0.001	67.4 ± 13.3	67.3 ± 13.3	0.44	68.3±16.8	67.5±16.8	<0.001
Female	9135 (54.9)	18270 (54.9)	>0.99	9065 (62.6)	90650 (62.6)	>0.99	5606 (56.2)	50454 (56.2)	>0.99
Socio economic s			<0.001			<0.001			0.002
low	7033 (42.2)	14411 (43.3)		5279 (36.4)	49843 (34.4)		3236 (32.4)	29426 (32.8)	
medium	4868 (29.2)	9105 (27.3)		4950 (34.2)	47295 (32.7)		4345 (43.5)	38803 (43.2)	
high	82 (0.5)	139 (0.4)		4255 (29.4)	47701 (32.9)		2384 (23.9)	21245 (23.7)	
missing	4664 (28.0)	9639 (29.0)					13 (0.1)	328 (0.4)	
Smoking	6725 (40.4)	11446 (34.4)	<0.001				4241 (42.5)	34786 (38.7)	<0.001
Obesity	55 (0.3)	120 (0.4)	0.649	673 (4.6)	5440 (3.8)	<0.001	2836 (28.4)	31812 (33.8)	<0.001
Diabetes	180 (1.1)	388 (1.2)	0.429	1066 (7.4)	8885 (6.1)	<0.001	2867 (28.7)	22831 (31.0)	<0.001
Hypertension	171 (1.0)	370 (1.1)	0.418	3286 (22.7)	26660 (18.5)	<0.001	5006 (50.2)	46437 (51.7)	0.003
Asthma	51 (0.3)	57 (0.2)	0.003	3280 (22.6)	3803 (2.6)	<0.001	2785 (27.9)	6913 (7.7)	<0.001
COPD	307 (1.8)	239 (0.7)	<0.001	3630 (25.1)	6044 (4.2)	<0.001	3367 (33.7)	5732 (6.4)	<0.001
Pulmonary fibrosis	NA	NA		633 (4.4)	562 (0.4)	<0.001	425 (4.3)	361 (0.4)	<0.001
Malignancy	38 (0.2)	95 (0.3)	0.283	1575 (10.9)	14083 (9.7)	<0.001	2241 (22.5)	16957 (18.9)	<0.001
IHD	58 (0.3)	125 (0.4)	0.695	1424 (9.8)	9159 (6.3)	<0.001	2312 (23.2)	18267 (20.3)	<0.001
CHF	342 (2.1)	532 (1.6)	<0.001	751 (5.2)	4221 (2.9)	<0.001	1095 (11.0)	7281 (8.1)	<0.001
CVA	134 (0.8)	313 (0.9)	0.144	1072 (7.4)	9747 (6.7)	0.002	1166 (11.7)	9797 (10.9)	0.019
Renal failure	173 (1.0)	414 (1.2)	0.051	393 (2.7)	2401 (1.7)	<0.001	1155 (11.6)	9160 (10.2)	<0.001
Liver disease	NA	NA		283 (2.0)	1774 (1.2)	<0.001	455 (4.6)	2540 (2.8)	<0.001

Rheumatoid arthri	NA	NA		516 (3.6)	1403 (1.0)	<0.001	295 (3.0)	1518 (1.7)	<0.001
# SCS prior 6 mor			<0.001			<0.001			<0.001
0	13430 (80.7)	30190 (90.7)		12698 (87.7)	139924 (96.6)		8344 (83.6)	83156 (92.6)	
1-2	2309 (13.9)	2150 (6.5)		1140 (7.9)	3284 (2.3)		1139 (11.4)	5271 (5.9)	
>=3	908 (5.5)	954 (2.9)		646 (4.5)	1632 (1.1)		495 (5.0)	1375 (1.5)	
# ICS prior 6 mon						<0.001			<0.001
0				10006 (69.1)	136181 (94.0)		7079 (70.9)	84505 (94.1)	
1-2				1283 (8.9)	3071 (2.1)		1302(13.0)	3015 (3.4)	
>=3				3195 (22.1)	5588 (3.9)		1597 (16.0)	2282 (2.5)	

CHF- congestive heart failure, CVA- past cerebrovascular accident, ICS- inhaled corticosteroid use. IHD- ischemic heart disease. SCS- systemic corticosteroid. SES- socioeconomic status. Smoking is defined as ever vs. never. *Danish registry substituted income tertiles for SES tertiles.

Figure 1 legend:

Hazard ratio estimates, adjusted for all covariates mentioned in the methods section were combined across studies using random effects meta-analysis model. Descriptive statatistics, crude and multivariable hazard ratio (HRs) for the association between bronchiectasis and outcomes are shown on the left, with Forest plots on the right for the following outcomes. A: risk of becoming PCR positive for SARS-COV2, bronchiectasis vs. no bronchiectasis. B: Risk for moderate to severe disease (Catalonia, Israel) or hospitalization within 30 days of SARS-CoV2 positive PCR (Denmark), bronchiectasis vs. no bronchiectasis. C. Mortality, bronchiectasis vs. no bronchiectasis

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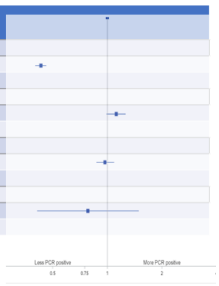
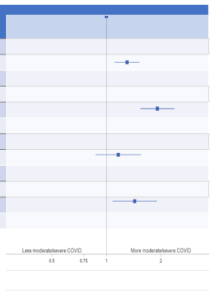
A. COVID-19 infection

Study site	Patient number	Outcome N	Crude HR (95% CI)	Multivariable HR (95% CI)
Catalonia				
Bronchiectasis	16647	1028	0.44 (0.41-0.47)	0.43 (0.40-0.46)
Controls	33294	4523	Ref	Ref
Denmark				
Bronchiectasis	14484	320	1.16 (1.03-1.30)	1.12 (0.99-1.26)
Controls	144840	2784	Ref	Ref
Israel				
Bronchiectasis	9978	337	0.96 (0.86-1.07)	0.97 (0.87-1.09)
Controls	89802	3178	Ref	Ref
All sites				
Bronchiectasis	41109	1685	0.79 (0.41-1.51)	0.78 (0.41-1.49)
Controls	267936	10485	Ref	Ref



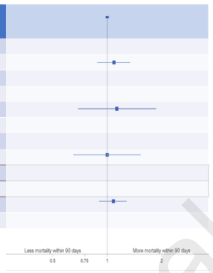
B. Moderate- severe COVID-19

Study site	Patient number	Outcome N	Crude HR (95% CI)	Multivariable HR (95% CI)
Catalonia				
Bronchiectasis	845	263	1.35 (1.16-2.0)	1.30 (1.11-1.52)
Controls	1690	405	Ref	Ref
Denmark				
Bronchiectasis	318	164	3.04 (2.52-3.68)	1.91 (1.54-2.37)
Controls	1590	306	Ref	Ref
Israel				
Bronchiectasis	337	67	1.51 (1.16-1.95)	1.16 (0.87-1.55)
Controls	3033	421	Ref	Ref
All sites				
Bronchiectasis	1500	494	1.84 (1.07-3.12)	1.43 (1.08-1.90)
Controls	6313	1132	Ref	



C. COVID-19 mortality

Study site	Patient number	Outcome N	Crude HR (95% CI)	Multivariable HR (95% CI)
Catalonia				
Bronchiectasis	845	143	1.15 (0.94-1.41)	1.09 (0.88-1.34)
Controls	1690	252	Ref	Ref
Denmark				
Bronchiectasis	318	22	1.38 (0.86-2.22)	1.13 (0.69-1.86)
Controls	1590	80	Ref	Ref
Israel				
Bronchiectasis	337	31	1.38 (0.94-2.01)	1.00 (0.65-1.53)
Controls	3033	207	Ref	Ref
All sites				
Bronchiectasis	1500	196	1.22 (1.03-1.44)	1.08 (0.90-1.28)
Controls	6313	539	Ref	Ref



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	3-4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3-4
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9
		(c) Summarise follow-up time (eg, average and total amount)	9-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-12
		(*b*) Report category boundaries when continuous variables were categorized	10-12
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.