

Bronchiectasis in Europe: data on disease characteristics from the European Bronchiectasis registry (EMBARC)



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Summary

Background Bronchiectasis is a heterogeneous, neglected disease with few multicentre studies exploring the causes, severity, microbiology, and treatment of the disease across Europe. This aim of this study was to describe the clinical characteristics of bronchiectasis and compare between different European countries.

Methods EMBARC is an international clinical research network for bronchiectasis. We report on a multicentre, prospective, observational, non-interventional, cohort study (the EMBARC registry) conducted across 27 European countries and Israel. Comprehensive clinical data were collected from adult patients (aged ≥ 18 years) at baseline and annual follow-up visits using electronic case report form. Data from individual countries were grouped into four regions (the UK, northern and western Europe, southern Europe, and central and eastern Europe according to modified EU EuroVoc classification). Follow-up data were used to explore differences in exacerbation frequency between regions using a negative binomial regression model.

Findings Between Jan 12, 2015, and April 12, 2022, 16963 individuals were enrolled. Median age was 67 years (IQR 57–74), 10335 (60.9%) participants were female and 6628 (39.1%) were male. The most common cause of bronchiectasis in all 16963 participants was post-infective disease in 3600 (21.2%); 6466 individuals (38.1%) were classified as idiopathic. Individuals with bronchiectasis experienced a median of two exacerbations (IQR 1–4) per year and 4483 (26.4%) patients had a hospitalisation for exacerbation in the previous year. When examining the percentage of all isolated bacteria, marked differences in microbiology were seen between countries, with a higher frequency of *Pseudomonas aeruginosa* and lower *Haemophilus influenzae* frequency in southern Europe, compared with higher *H influenzae* in the UK and northern and western Europe. Compared with other regions, patients in central and eastern Europe had more severe bronchiectasis measured by the Bronchiectasis Severity Index (51.3% vs 35.1% in the overall cohort) and more exacerbations leading to hospitalisations (57.9% vs 26.4% in the overall cohort). Overall, patients in central and eastern Europe had an increased frequency of exacerbations (adjusted rate ratio [RR] 1.12, 95% CI 1.01–1.25) and a higher frequency of exacerbations leading to hospitalisations (adjusted RR 1.71, 1.44–2.02) compared with patients in other regions. Treatment of bronchiectasis was highly heterogeneous between regions.

Interpretation Bronchiectasis shows important geographical variation in causes, microbiology, severity, and outcomes across Europe.

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Introduction

Bronchiectasis is a chronic condition described as “one of the most neglected diseases in respiratory medicine”.^{1–3} Patients experience chronic cough, sputum production, dyspnoea, fatigue, and recurrent exacerbations.⁴ The prevalence of bronchiectasis is increasing worldwide, with prevalence estimates from the UK of up to 566 per 100 000 population in 2013 and 174 per 100 000 from a recent study in China.^{5–7} Bronchiectasis represents the final common pathway of a number of underlying diseases and in many cases an underlying condition is never identified.⁸ Severe

infections such as pneumonia and tuberculosis are reported to be the most common causes of bronchiectasis, but the prevalence of bronchiectasis has increased worldwide over the past 20 years whereas the incidence of severe childhood infections and tuberculosis have declined.^{5,9}

Bronchiectasis affects every age group, from young children to older adults and has a highly variable clinical presentation.¹⁰ This heterogeneity of disease is regarded as one of the most important challenges in developing new treatments.¹¹ Patients have different demographics, clinical symptoms, lung function patterns, comorbidities,

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Research in context

Evidence before this study

We searched PubMed from inception until May 1, 2022, for articles related to causes, microbiology, severity, and treatment of bronchiectasis. We identified 5598 articles. Although we identified a marked increase in studies into the epidemiology of bronchiectasis in recent years, increasing from 193 references in 2011 to 406 in 2021, most studies were single centre and of small sample size. Prospective registry data was identified from Europe, the USA, Australia, India, and Korea, the largest of which had a sample size of 2596 patients and was limited to a small number of western European countries. There were no studies identified describing the causes, microbiology, severity of disease and treatment of bronchiectasis across Europe and particularly a paucity of data from central and eastern Europe. There were no studies exploring differences in patient characteristics between different regions. Only one of the registries reported any long-term follow-up data for participants. In summary, large-scale characterisation of the causes, severity, microbiology, and treatment of bronchiectasis in Europe with comparisons between countries and prospective long-term follow-up is not available.

Added value of this study

We report on the largest prospective registry of bronchiectasis globally with an initial report of 16 963 patients from 27 European countries and Israel. We describe the frequency of different aetiologies, showing that 38.1% of patients are classified as idiopathic and 21.2% as post-infective. We describe the burden of disease including the frequency of exacerbation and hospitalisation, patterns of lung function impairment and overall severity of disease. We show that *Pseudomonas aeruginosa* and *Haemophilus influenzae* are the most common pathogens and that marked differences in microbiology were seen between countries with a higher frequency of *P aeruginosa* and lower *H influenzae* frequency in southern Europe and higher

H influenzae in the UK and Northern Europe. Patients in Eastern Europe had more severe bronchiectasis, received fewer drug treatments, and had increased exacerbations during follow-up. Treatment of bronchiectasis was highly heterogeneous between regions and was not evidence based.

Implications of all the available evidence

There are no licensed therapies for bronchiectasis and scarce evidence to guide treatment. We show a high level of unmet need. The majority of patients have idiopathic or post-infective disease. We report a high burden of disease associated with bronchiectasis in Europe including frequent exacerbations and hospitalisations, poor quality of life, and high rates of infection with Gram-negative bacteria emphasising the need for better evidence to guide investigation and treatment. *P aeruginosa* is an antibiotic resistant pathogen associated with worse outcomes in bronchiectasis. The finding that this organism is much more common in southern Europe requires further investigation and could help to guide more intensive efforts to identify and treat *P aeruginosa* in regions of high prevalence. We show remarkable variation in the treatment of bronchiectasis between countries illustrating absence of clear evidence for many interventions. These data should inform future guidelines, stimulate efforts to better implement existing evidence-based treatment such as airway clearance and macrolides, and encourage future randomised trials. Inequality in access to evidence-based treatment can lead to worse outcomes and we show lower receipt of treatments as well as greater disease severity and increased exacerbations in central and eastern European countries, which emphasise the importance of developing strategies to improve outcomes in these regions where historically bronchiectasis has received little attention. This is the first report from the EMBARC registry which has the capacity to provide extensive insights into the epidemiology of bronchiectasis.

underlying causes, microbiology, and underlying inflammatory profiles.^{12–14} There are no licensed treatments for bronchiectasis and bronchiectasis guidelines are based primarily on expert opinion or low quality evidence from small randomised controlled trials.⁸ It is therefore probable that patients vary in their characteristics geographically and also receive very different health care and treatments in different parts of the world. There are scarce data published from patients with bronchiectasis in central and eastern Europe in comparison with western and southern Europe and North America.¹⁵ It is important for future therapeutic development to understand differences in patient characteristics, treatment, and outcomes across the world. For example, inhaled dry powder ciprofloxacin was tested in two replicate randomised controlled trial programmes. In RESPIRE 1 which was conducted primarily in western Europe and North America, a significant benefit of treatment was observed.¹⁶ In RESPIRE 2, which had an

identical design but which included a much larger proportion of patients from eastern Europe and Asia, the exacerbation rate was markedly lower, patients had different characteristics, and there was no evidence of treatment benefit.¹⁷ Similar inconsistent results have been observed in other trial programmes such as the ORBIT trials of inhaled liposomal ciprofloxacin.¹⁸

In 2015, the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC), an international research network, established the EMBARC registry as a pan-European registry for patients with bronchiectasis to investigate the characteristics of patients with bronchiectasis, establish the burden of disease and to gather long term follow-up data to examine determinants of outcome.¹ In this report we describe the characteristics of patients with bronchiectasis across Europe, examine differences in characteristics between countries and explore possible differences in clinical outcomes.

Methods

Study design

The EMBARC registry is an ongoing multicentre, prospective, observational cohort study enrolling consecutive adult patients with bronchiectasis across Europe and Israel. The study is open to both primary and secondary care, and from specialised and non-specialised centres; with the majority of patients being recruited from secondary care. Patients give informed consent to participate and data are collected at baseline (recruitment) and up to 5 years at annual follow-up visits (± 3 months). Data are collected across a series of domains including: demographics; comorbidities; aetiological testing; lung function; exacerbations; disease impact; quality of life (QoL); microbiology; radiology; and treatment. The protocol for the registry has been previously published.¹ The study is non-interventional. Patients are managed according to local practice with no interference from the registry team.

The study received central ethical approval from the Multicentre Research Ethics Committee in the UK on Jan 8, 2015 (14/SS/1101) and the study is sponsored by the University of Dundee, Dundee, UK. Recruitment began on Jan 12, 2015, and is ongoing. The database was locked on May 1, 2022, for this analysis. The registry was developed in accordance with recommendations on the design, implementation, governance, and long-term sustainability of disease registries in the EU, as proposed by the European Platform for Rare Disease Registries consortium and EU Committee of Experts on Rare Diseases.¹⁹

Participants

For inclusion patients must have a primary diagnosis of bronchiectasis and meet the inclusion criteria of: a clinical history consistent with bronchiectasis (current or previous history of cough, chronic sputum production, or recurrent respiratory infections); and computed tomography of the chest showing bronchiectasis (bronchial dilatation) affecting one or more lobes. The exclusion criteria were: bronchiectasis due to known cystic fibrosis; age younger than 18 years; inability or unwillingness to provide informed consent; traction bronchiectasis due to interstitial lung disease without free standing bronchiectasis and previous heart and lung transplantation.

Data collection

Data were collected by site staff for patients during stability, defined as the absence of exacerbation treated with antibiotics, with additional data collection during exacerbations. The causes of bronchiectasis were determined and reported by the physician caring for the patient. Extensive data were collected on the aetiological testing performed by the treating clinician, based on the testing recommended by consensus guidelines and, therefore, the underlying basis for an aetiological diagnosis was collected and could be validated.

Exacerbations were defined as an acute deterioration in symptoms requiring antibiotic therapy as determined by the treating clinician. Spirometry was recorded with % predicted values calculated using European Community of Coal and Steel equations²⁰ implemented centrally. The registry recorded data on spirometry before and after bronchodilator. Breathlessness was evaluated using the modified Medical Research Council Dyspnoea scale. QoL was assessed using the QoL-Bronchiectasis Questionnaire (version 3.1).²¹ Sputum microbiology was recorded for samples sent in stable state and during exacerbation in the previous 12 months with results from local laboratories. Severity of bronchiectasis on CT scans were scored using the modified Reiff score.²² Disease severity was evaluated using the Multidimensional Bronchiectasis Severity Index (BSI) and the FACED score.²³ Patients who are still under follow-up with their respective clinical teams are followed up annually with data collection including changes in medication, exacerbation frequency, and exacerbation leading to hospitalisations. The registry protocol required a minimum dataset is collected for patients to be enrolled thereby minimising missing data. A small number of variables could be missing, such as lung function testing and microbiology; the extent of missing data are outlined in the results section.

Statistical analysis

Descriptive characteristics of the cohorts were compared using t-test or Mann-Whitney U test for comparing two groups or the χ^2 or Fishers exact test used for comparing categorical data between groups. For analysis by region and country per protocol, European regions were divided according to a modification of the EU EuroVoc classification into northern and western Europe, southern Europe, and central and eastern Europe for the purposes of regional analysis (appendix 9 p 3). Data from Israel was pooled with southern Europe. Due to high patient recruitment in the UK we present data for the UK separately from western Europe and as the largest group, the UK was used as the reference for analyses comparing exacerbation rates between regions. Missing data were common for some tests which are not universally performed in clinical practice (eg, microbiology) and complete case analyses are presented for these parameters. For calculation of severity scores patients without microbiology data were assumed to be non-infected in line with the original derivation studies.²⁴ For analyses of long-term clinical outcomes, a negative binomial model was used to evaluate long-term exacerbations and exacerbations leading to hospitalisations with time of follow-up as an offset.²⁵ Analyses were conducted adjusting for confounders based on clinical relevance and past literature.^{24,26,27} We conducted separate adjusted analysis incorporating patient characteristics and fully adjusted analyses incorporating patient characteristics and treatments. Prespecified subgroup analyses were conducted excluding patients with a codiagnosis of COPD

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For the EU EuroVoc see <https://op.europa.eu/en/web/eu-vocabularies>

See Online for appendix 9

	EMBARC cohort (n=16 963)	UK (n=8163)	Southern Europe (n=4295)	Northern and western Europe (n=3444)	Central and eastern Europe (n=1061)
Age, years	67 (57–74)	69 (61–75)	66 (54–74)	65 (52–73)	62 (53–70)
Age >65 years	9943 (58.6%)	5465 (66.9%)	2174 (50.6%)	1841 (53.5%)	463 (43.6%)
Female	10 335 (60.9%)	4938 (60.5%)	2766 (64.4%)	2101 (61.0%)	530 (50.0%)
Male	6628 (39.1%)	3225 (39.5%)	1529 (35.6%)	1343 (39.0%)	531 (50.0%)
BMI, kg/m ² *	24.9 (21.7–28.7)	25.7 (22.4–29.8)	24.3 (21.4–27.7)	23.8 (21.4–27.7)	24.8 (21.2–28.4)
Comorbidities					
Cardiovascular diseases	5509 (32.5%)	2413 (29.6%)	1397 (32.5%)	1135 (33.0%)	564 (53.2%)
Stroke	600 (3.5%)	388 (4.8%)	79 (1.8%)	101 (2.9%)	32 (3.0%)
Liver disease	103 (0.6%)	35 (0.4%)	15 (0.3%)	40 (1.2%)	13 (1.2%)
Osteoporosis	2228 (13.1%)	1255 (15.4%)	460 (10.7%)	398 (11.6%)	115 (10.8%)
Depression	2377 (14.0%)	1401 (17.2%)	493 (11.5%)	350 (10.2%)	133 (12.5%)
Anxiety	2428 (14.3%)	1290 (15.8%)	660 (15.4%)	339 (9.8%)	139 (13.1%)
Neoplastic disease	1863 (11.0%)	885 (10.8%)	435 (10.1%)	429 (12.5%)	114 (10.7%)
Chronic renal failure	667 (3.9%)	280 (3.4%)	173 (4.0%)	199 (5.8%)	15 (1.4%)
Diabetes	1724 (10.2%)	880 (10.8%)	403 (9.4%)	302 (8.8%)	139 (13.1%)
Asthma	5267 (31.0%)	3208 (39.3%)	811 (18.9%)	1046 (30.4%)	202 (19.0%)
COPD	4324 (25.5%)	2225 (27.3%)	828 (19.3%)	862 (25.0%)	409 (38.5%)
Smoking					
Never	9096 (53.6%)	4191 (51.3%)	2436 (56.7%)	1942 (56.4%)	527 (49.7%)
Ex-smoker	6785 (40.0%)	3591 (44.0%)	1501 (34.9%)	1328 (38.6%)	365 (34.4%)
Current	1082 (6.4%)	381 (4.7%)	358 (8.3%)	174 (5.1%)	169 (15.9%)
Severity of illness					
Modified MRC dyspnoea score	1 (0–2)	1 (1–2)	1 (0–2)	1 (0–2)	2 (1–3)
Does not produce daily sputum	4752 (28.0%)	2203 (27.0%)	1598 (37.2%)	947 (27.5%)	302 (28.5%)
Quality of life bronchiectasis respiratory symptom score†	63 (44–77.8)	59.3 (40.7–77.8)	70.4 (51.9–83.3)	62.9 (44.4–77.7)	59.3 (40.7–74.1)

Data are median (IQR) and n (%). COPD=chronic obstructive pulmonary disease. MRC=Medical Research Council. Data were complete for all 16963 participants except where indicated. *There were 15 792 participants in the EMBARC cohort (7461 in UK, 4113 in southern Europe, 3182 in western and northern Europe, and 1036 in central eastern Europe) with available data for BMI. †There were 11 152 participants in the EMBARC cohort (7131 in UK, 1130 in southern Europe, 2367 in western and northern Europe, and 524 in central eastern Europe) with available quality of life bronchiectasis respiratory symptom score.

Table 1: Patient characteristics overall and by European region

or asthma, and based on severity of disease using the bronchiectasis severity index. Analyses were conducted using SPSS (version 22). Due to the large sample size of the EMBARC registry, significant differences might be observed at the conventional $p < 0.05$ threshold even where clinically meaningful differences are not observed. We therefore took a conservative approach to hypothesis testing. Data are presented descriptively for the majority of outcomes with p-values presented only where they aid interpretation of the data. Results of the negative binomial regression analysis are presented as unadjusted and adjusted rate ratios (RR) with 95% CIs without p-values.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation or writing of the Article.

Results

Between Jan 12, 2015, and April 12, 2022, 19 324 cases were valid and eligible for analysis. 2361 patients from

non-European countries were excluded and finally 16 963 patients from 27 European countries and Israel were included in this analysis. The largest enrolling countries were the UK with 8163 (48.1%) patients enrolled followed by 1657 (9.8%) patients from Italy, 1025 patients from Germany (6.0%) and 1000 patients from Spain (5.9%). A breakdown of the distribution of patients by country is shown in appendix 9 (p 3). 240 primary and secondary, specialised and non-specialised, care centres in total contributed patients with the largest centre contributing 777 participants.

Table 1 shows a description of the patient population in total and by region. Patients with bronchiectasis had a median age of 67 years (IQR 57–74) and were predominantly female (10 335 [60.9%] of 16 963) with a high frequency of non-pulmonary comorbid illnesses such as cardiovascular disease, depression, osteoporosis and diabetes. Differences between regions included younger age, more men, high rates of cardiovascular comorbidity, chronic obstructive pulmonary disease (COPD), and current smoking in central and eastern

Europe. Patient characteristics were more similar in the UK, southern Europe, and northern and western Europe.

Figure 1 shows the distribution of causes across the patient population and by region.

A cause was not identified in 6466 (38.1%) of 16 963 participants and these were classified as idiopathic disease. The most common identified cause was post-infective disease in 3600 (21.2%) of 16 963 participants. There were significant differences in the frequency of aetiologies across all four regions (appendix 9 p 4) and between countries (figure 1). In regional comparisons, the UK and southern Europe had a higher frequency of idiopathic disease. Allergic bronchopulmonary aspergillosis (ABPA) was more common in the UK and north and western Europe and uncommon as a cause of bronchiectasis in southern Europe and central and eastern Europe. Immunodeficiency was more common in northern and western Europe and southern Europe, whereas central and eastern Europe had a higher frequency of post-infective and COPD associated bronchiectasis (appendix 9 p 4). For the 3600 patients with post-infective causes, pneumonia was the most common documented infection in 2342 (65.1%), followed by childhood respiratory infections in 1373 (38.1%) and pertussis in 805 (22.4%), with many patients having more than one documented infection.

The country map (appendix 9 p 5) shows that tuberculosis associated bronchiectasis was most frequent in southern Europe and central and eastern Europe (with the highest proportion of cases in Moldova at 57 [20.2%] of 282 and Türkiye at 42 [18.9%] of 222, and Portugal at 42 [19.8%] of 212) in line with the countries that have the highest incidence of tuberculosis in general. Connective tissue disease and primary ciliary dyskinesia were most frequently reported in northern and western Europe.

Lung function data were available for 15 277 patients (90.1%). The median FEV₁ across the whole population was 76.9% of predicted value. Airflow obstruction was the most common spirometric pattern (5919 [34.9%] of 16 963) followed by normal spirometry (5300 [31.2%]). Just under a quarter of the population had preserved ratio impaired spirometry (PRISm). Detailed lung function data are shown in table 2. Comparing the patterns of lung function impairment between regions showed the lowest FEV₁ in central and eastern Europe ($p < 0.0001$) and highest lung function parameters in southern Europe. The proportion of patients with airflow obstruction was also highest in central and eastern Europe ($p < 0.0001$, table 2). The median FEV₁ (% of predicted value) by country showed lower median FEV₁ consistently across central and eastern Europe (appendix 9 p 7). Patients from central and eastern Europe showed lower FEV₁% predicted and absolute FEV₁ across age groups in both males and females as shown by the regression analysis (appendix 9 p 8). The differences in lung function between different countries are shown in appendix 9 (p 6). In

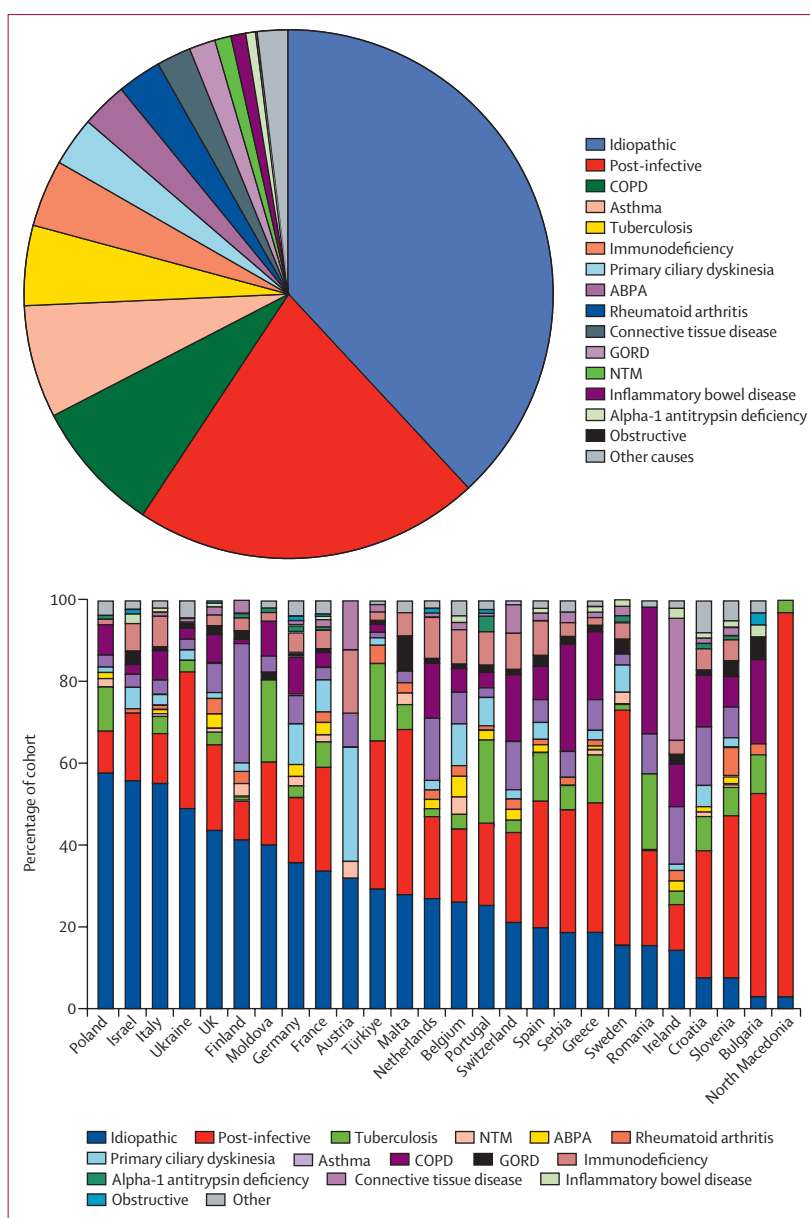


Figure 1: Underlying causes of bronchiectasis in the EMBARC cohort

(A) Underlying causes of bronchiectasis in the overall cohort (n=16 963). (B) Underlying causes of bronchiectasis analysed by country. COPD=chronic obstructive pulmonary disease. ABPA=allergic bronchopulmonary aspergillosis. GORD=gastro-oesophageal reflux disease. NTM=non-tuberculous mycobacterial infection.

regional comparisons, no large differences in time since bronchiectasis diagnosis were observed (appendix 9 p 7).

12 152 patients had at least one sputum or bronchoalveolar lavage sample available for analysis for microbiology (71.6% of the overall cohort). 7648 patients (45.1%) did not have a sputum sample sent in stable state in the previous 12 months and therefore only had samples from exacerbation available. Microbiology results in stable state and including all samples are shown in appendix 9 (p 8–9). Examining bacteria isolated from sputum samples the most frequent was

	EMBARC cohort (n=16 963)	UK (n=8163)	Southern Europe (n=4295)	Northern and western Europe (n=3444)	Central and eastern Europe (n=1061)
Lung function parameters					
Number of participants with available FEV ₁ and FVC data	15 290	7037	3968	3288	997
FEV ₁ , L	1.78 (1.26–2.38)	1.71 (1.23–2.30)	1.84 (1.28–2.43)	1.90 (1.37–2.50)	1.64 (1.06–2.29)
FEV ₁ % predicted	76.9 (56.0–96.7)	75.4 (55.8–94.8)	82.6 (59.9–105.5)	76.9 (57.1–94.9)	63.4 (43.6–88.7)
FVC, L	2.65 (2.04–3.35)	2.60 (2.04–3.30)	2.62 (2.00–3.29)	2.81 (2.17–3.52)	2.61 (1.94–3.39)
FVC % predicted	91.4 (73.7–107.8)	91.2 (74.6–106.6)	93.6 (74.7–113.9)	91.4 (74.3–106.5)	81.9 (62.2–101.4)
FEV₁% predicted group					
>80%	6819 (40.2%)	3058 (37.5%)	1915 (44.6%)	1501 (43.6%)	345 (32.5%)
50–79%	5475 (32.3%)	2647 (32.4%)	1329 (30.9%)	1187 (34.5%)	312 (29.4%)
30–49%	2334 (13.8%)	1074 (13.2%)	536 (12.5%)	473 (13.7%)	251 (23.7%)
<30%	618 (3.6%)	258 (3.2%)	144 (3.4%)	127 (3.7%)	89 (8.4%)
Missing	1717 (10.1%)	1126 (13.8%)	371 (8.6%)	156 (4.5%)	64 (6.0%)
Lung function pattern					
Obstruction	5919 (34.9%)	2949 (36.1%)	1270 (29.6%)	1233 (35.8%)	467 (44.0%)
PRISm	4058 (23.9%)	1888 (23.1%)	1017 (23.7%)	890 (25.8%)	263 (24.8%)
Normal spirometry	5300 (31.2%)	2317 (28.4%)	1606 (37.4%)	1121 (32.5%)	256 (24.1%)
Unknown	1686 (9.9%)	1009 (12.4%)	402 (9.4%)	200 (5.8%)	75 (7.1%)
Data are n (%) or median (IQR). FVC=forced vital capacity. PRISm=preserved ratio impaired spirometry. Obstruction is defined as FEV ₁ /FVC ratio <0.7. PRISm is defined as an FEV ₁ <80% of predicted with FEV ₁ /FVC ratio >0.7.					
Table 2: Lung function overall and by region					

Pseudomonas aeruginosa in 3047 (25.1%) followed by *Haemophilus influenzae* in 2866 (23.6%), *Enterobacteriaceae* in 1929 (15.9%), *Staphylococcus aureus* in 1044 (8.6%), *Streptococcus pneumoniae* in 1032 (8.5%), and *Moraxella catarrhalis* in 652 (5.4%) of all 12152 patients (figure 2A). It was common for patients to isolate more than one pathogen over the course of a year; 2791 patients (36.1%) out of 7731 with positive sputum samples isolated more than one major pathogen. Analysing the results of sputum samples sent in stable state only (n=9226), the most commonly isolated pathogen was *P aeruginosa* 2013 (21.8%), followed by *H influenzae* 1779 (19.2%), *Enterobacteriaceae* 1212 (13.1%), *S aureus* 718 (7.8%), *S pneumoniae* 533 (5.8%), and *M catarrhalis* 340 (3.7%). There were differences between regions in the proportions of patients with sputum samples sent with low sampling during stable state in central and eastern Europe, but higher sampling at exacerbation (appendix 9 p 9). The sputum samples sent and frequency of bacterial detection by country are shown in appendix 9 (p 10–11). The proportions of patients where a bacterium was isolated were similar between regions (appendix 9 p 9) and so the primary comparisons between regions were examining the distribution of organisms as a proportion of all bacteria isolated. Regardless of the denominator used, there were marked differences in the frequency of bacterial isolation between different regions (appendix 9 p 14).

Examining the percentage of all isolated bacteria that were *P aeruginosa* revealed a strong geographical effect

whereby patients from the majority of southern European countries (Spain, Italy, Austria, Bulgaria, Greece, Italy, Malta, Spain and Türkiye) had *P aeruginosa* infection in more than 50% of cases (figure 2B). Those countries where *P aeruginosa* accounted for less than 40% of cases were predominantly in northern and western Europe as well as central and eastern Europe (p<0.0001, comparing the proportions of patients isolating *P aeruginosa* between regions by χ^2 test).

H influenzae was more common than *P aeruginosa* in UK, Ireland, Netherlands, Israel, Denmark, North Macedonia, Portugal, Switzerland, and Slovenia while *P aeruginosa* was more common in most other countries. Differences between countries are shown in figure 2C and in full in appendix 9 (p 12–13). The comparison of microbiology profiles between regions is also presented in appendix 9 (p 14). The distribution of other pathogens was also different between regions *P aeruginosa* and *H influenzae* were the most common organisms in UK and northern and western Europe, whereas *Enterobacteriaceae* were more common than *H influenzae* in southern and eastern and central Europe and second only to *P aeruginosa* (all described differences p<0.0001).

Patients with bronchiectasis showed a high burden of disease. In terms of exacerbations, 4163 (24.5%) of 16963 patients had no exacerbations in the year before the study, 3163 (18.6%) had one exacerbation, 3053 (18.0%) had two exacerbations (IQR 1–4) and 6584 (38.8%) had three or more exacerbations per year (appendix 9 p 15). 4483 patients (26.4%) had at least one hospital admission

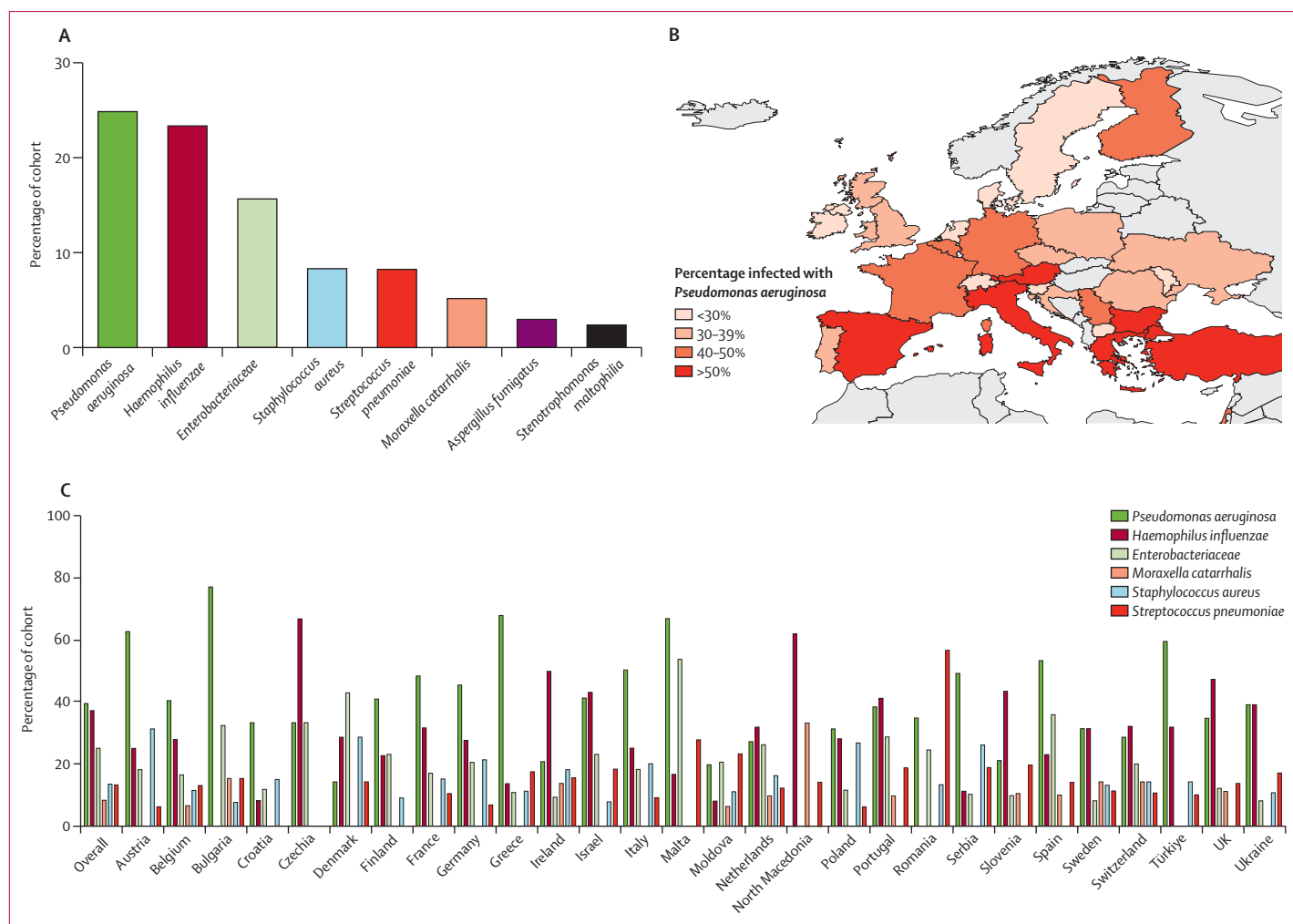


Figure 2: Microbiology of bronchiectasis in the EMBARC cohort

(A) Microbiology of the overall EMBARC cohort (n=16 963) showing the percentage of patients who isolated the most common pathogens; this analysis includes any isolation of the pathogen in either a sample taken when stable or at exacerbation (any sample). (B) Percentage of patients in different countries isolating *Pseudomonas aeruginosa* in any sample over the previous year; the denominators are patients isolating at least one pathogenic microorganism during the previous year. (C) Percentage of patients in different countries from whom any one of the six most common pathogens or groups of pathogens was isolated from any sample over preceding 1 year; the denominators are patients from whom least one pathogenic microorganism was isolated from any sputum sample during the previous year.

for an exacerbation in the year before the study, 2886 (17.0%) of 16 963 patients had one hospitalisation, 969 (5.7%) had two hospitalisations and 628 (3.7%) had three or more hospitalisations.

Using the BSI to assess disease severity, 4960 patients (29.2%) had mild bronchiectasis, 6054 (35.7%) had moderate bronchiectasis and 5949 (35.1%) had severe bronchiectasis (appendix 9 p 15). Data for the FACED score are shown in appendix 9 (p 15).

Comparing the burden of illness between different regions there were striking differences in terms of severity of disease and exacerbations. Patients were more likely to have a history of exacerbation leading to hospitalisations in central and eastern Europe (57.9% with at least one hospitalisation, compared with 26.4% in the cohort overall, appendix 9 p 15). Figure 3A shows hospitalisation

by country showing excess hospitalisations were found in nearly all central and eastern European countries. The median BSI was 9 (IQR 5–12) in central and eastern Europe compared with 6 (IQR 4–10) in both southern Europe and northern and western Europe and 7 (IQR 4–10) in the UK ($p < 0.0001$). A higher proportion of patients had severe bronchiectasis by the BSI in central and eastern Europe compared with all other regions—the proportion with severe bronchiectasis was 51.3% in central and eastern Europe compared to 34.5%, 34.3% and 32.7% in the other regions and 35.1% in the overall cohort ($p < 0.0001$, appendix 9 p 15). Figure 3B shows that severity of bronchiectasis was higher in western and central and eastern European countries. In terms of radiological severity, the median Reiff score was 4 (2–6) in central and eastern Europe and in southern Europe

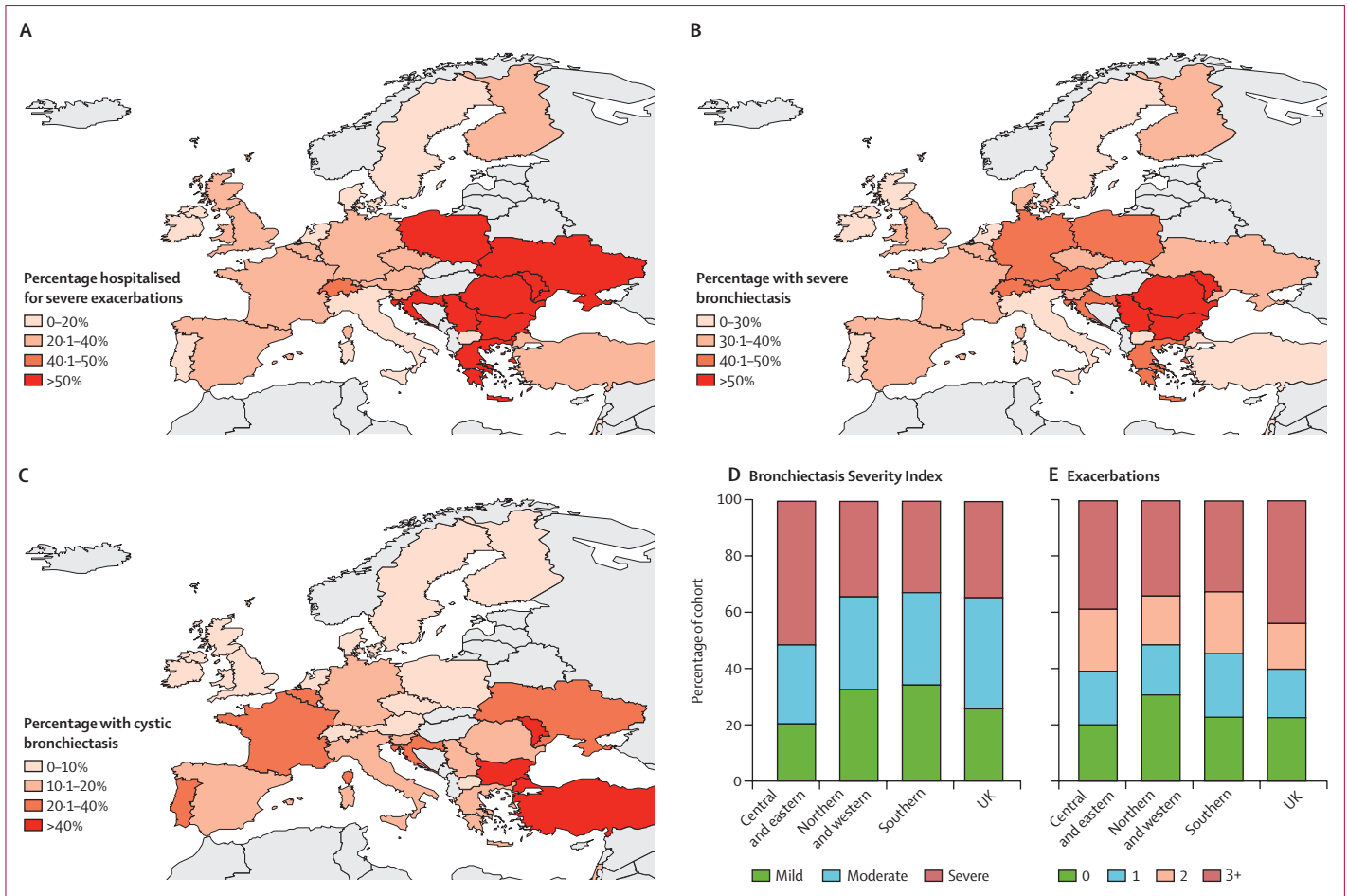


Figure 3: Severity of disease and exacerbations of bronchiectasis across Europe

(A) Percentage of patients in each country who experienced at least one exacerbation leading to hospitalisation in the year preceding baseline. (B) Percentage of patients with severe bronchiectasis using the Bronchiectasis Severity Index. (C) Percentage of patients with cystic bronchiectasis reported on CT scan across difference regions. (D) Proportion of patients with mild or moderate and severe bronchiectasis using the BSI across regions. (E) Proportion of patients with different exacerbation frequencies between regions.

compared with 3 (2–6) in the UK and northern and western Europe ($p < 0.0001$ for Kruskal-Wallis test comparing the medians across all four regions). The frequency of cystic bronchiectasis was markedly higher in central and eastern and southern Europe (figure 3C). The overall distribution of severity (figure 3D) and exacerbations (figure 3E) are shown. Frequent exacerbations with 3 or more exacerbations in the previous year were most frequent in the UK and central and eastern Europe.

The most commonly used treatments in patients with bronchiectasis in the EMBARC cohort were inhaled corticosteroids and long-acting beta agonists used by 8700 (51.3%) and 8632 (50.9%) of the overall cohort ($n=16\,963$) respectively (table 3). 8539 patients did not have a history of COPD or asthma. Inhaled corticosteroids were used by 2595 patients (30.4%) without documented COPD or asthma. In the entire cohort, the most common prophylactic antibiotics used in the entire cohort were macrolides, used by 2940 (17.3%) participants, and inhaled antibiotics, used by

1310 (7.7%) participants. The most commonly used mucoactive drugs were oral carbocysteine/*N*-acetylcysteine mucolytics and nebulised hypertonic saline, used by 2910 (17.2%) and 1454 (8.6%) participants respectively. 8739 (51.5%) patients reported using a form of regular airway clearance at baseline. Most patients used manual airway clearance techniques such as active cycle of breathing technique. Airway clearance devices were used by 2748 (16.2%) patients.

We observed remarkable geographical variation in treatment patterns as shown in table 3. Inhaled corticosteroid use was most common in the UK compared with other regions. Leukotriene receptor antagonists were used most frequently in the UK, and theophylline use was most common in central and eastern Europe. Among the antibiotics, macrolide use was most frequent in northern and western Europe (840 [24.4%] of 3444) and the UK (1615 [19.8%] of 8163) and uncommon in central and eastern Europe. Inhaled antibiotic use was more common in northern and western Europe and was

uncommon in central and eastern Europe (table 3). Among mucoactive drugs, even more striking differences were observed. Carbocisteine or n-acetylcysteine were used in 29.3% (2389 of 8163) of UK patients but in less than 10% of patients in all other regions. Hypertonic saline was used in 662 (19.2%) of 3444 patients in northern and western Europe and was used in less than 10% of patients in other regions (table 3).

Commonly used medications by country are reported in appendix 9 (p 16). Inhaled corticosteroid use was relatively consistent between countries with 30–60% of patients receiving inhaled corticosteroids in most countries (appendix 9 p 18). There was much greater variation in inhaled antibiotic use with 200 (20%) of 1000 patients in Spain receiving inhaled antibiotics and only 19 (1.1%) of 1657 patients in Italy despite similarly high rates of *P aeruginosa* infection (appendix 9 p 18). Macrolide use was high in most northern and western and southern European countries (appendix 9 p 19). Germany, Austria, Israel, and the Netherlands showed high rates of hypertonic saline use (appendix 9 p 16).

Antibiotic use according to the presence or absence of *P aeruginosa* is reported in appendix 9 (p 17). In patients with a history of *P aeruginosa* infection inhaled antibiotic use was similar in the UK, southern Europe, and northern and western Europe. Macrolide use was high in the UK (>30%) and western European countries such as Belgium, Netherlands, Ireland, and France (>20%) but was lower in southern Europe. All treatments were less common in central and eastern Europe. In patients without a history of *P aeruginosa*, inhaled antibiotic use was uncommon but macrolide use was similarly high in UK and northern and western Europe (appendix 9 p 17).

Having observed that patients in central and eastern Europe were more likely to have severe cystic bronchiectasis and were less likely to receive evidence-based treatments, we investigated whether this translated into more exacerbations during follow-up. For this analysis of regional differences in exacerbations, we included 9978 patients who had at least 1 year of follow-up data. Exacerbation data were available for 652 patients from central and eastern Europe (median of 1168 days of observation per participant), 1831 patients from north and western Europe (median 1095 days of follow-up), 1838 patients from southern Europe (1096 days of follow-up) and 5657 patients from the UK (median 1172 days of follow-up). We compared the outcomes of patients across the four regions and the results are shown in table 4. As the largest group, patients from the UK were used as the reference. Compared with this reference, patients from northern and western Europe had a lower frequency of exacerbations during follow-up, both in unadjusted and adjusted analyses (adjusted RR 0.72, 95% CI 0.66–0.77). Patients in Northern and western Europe did not have a reduced risk of exacerbation leading to hospitalisations (1.05, 0.93–1.18). Patients in southern Europe had a lower risk of exacerbation leading

	EMBARC cohort (n=16 963)	UK (n=8163)	Southern Europe (n=4295)	Northern and western Europe (n=3444)	Central and eastern Europe (n=1061)
Inhaled corticosteroid	8700 (51.3%)	4796 (58.8%)	1779 (41.4%)	1630 (47.3%)	395 (37.2%)
LABA	8632 (50.9%)	4311 (52.8%)	2104 (49.0%)	1764 (51.2%)	453 (42.7%)
LAMA	4707 (27.7%)	2231 (27.3%)	1278 (29.8%)	911 (26.5%)	287 (27.0%)
LTRA	1007 (5.9%)	665 (8.1%)	135 (3.1%)	169 (4.9%)	38 (3.6%)
Theophylline	483 (2.8%)	298 (3.7%)	53 (1.2%)	70 (2.0%)	62 (5.8%)
Antibiotic treatments					
Inhaled antibiotic	1310 (7.7%)	620 (7.6%)	365 (8.5%)	306 (8.9%)	19 (1.8%)
Macrolide	2940 (17.3%)	1615 (19.8%)	475 (11.1%)	840 (24.4%)	10 (0.9%)
Other oral antibiotic prophylaxis	794 (4.7%)	574 (7.0%)	99 (2.3%)	101 (2.9%)	20 (1.9%)
Cyclical antibiotics	604 (3.6%)	297 (3.6%)	127 (3.0%)	116 (3.4%)	64 (6.0%)
Mucoactive drugs					
Carbocisteine or N-acetylcysteine	2910 (17.2%)	2389 (29.3%)	208 (4.8%)	256 (7.4%)	57 (5.4%)
Hypertonic saline	1454 (8.6%)	537 (6.6%)	224 (5.2%)	662 (19.2%)	31 (2.9%)
Isotonic saline	872 (5.1%)	356 (4.4%)	92 (2.1%)	373 (10.8%)	51 (4.8%)
Mannitol	4 (0%)	2 (0.0%)	0 (0%)	2 (0.1%)	0 (0%)
DNAse	75 (0.4%)	36 (0.4%)	19 (0.4%)	12 (0.3%)	8 (0.8%)
Sodium hyaluronate	24 (0.1%)	2 (0.0%)	16 (0.4%)	5 (0.1%)	1 (0.1%)

Data are n (%). LABA=long-acting beta agonist. LAMA=long-acting muscarinic antagonist. LTRA=leukotriene receptor antagonist.

Table 3: Commonly used treatments between different European regions

to hospitalisations in unadjusted analyses but this was not seen after covariate adjustment. Patients in central and eastern Europe, however, had an increased frequency of exacerbations (1.12, 1.01–1.25) and a high frequency of exacerbation leading to hospitalisations (1.71, 1.44–2.02) even after covariate adjustment (table 4). Unadjusted RRs for exacerbations across regions in different severity groups suggesting higher rates in southern Europe and central and eastern Europe were primarily seen in patients with mild to moderate severity of the disease according to the BSI score (appendix 9 p 20).

Discussion

The EMBARC registry is, to the best of our knowledge, the largest and most comprehensive prospective dataset of patients with bronchiectasis globally. This first report of data from the registry provides a comprehensive description of the disease from 28 countries.

The most frequent causes of bronchiectasis were idiopathic and post-infective and combined these causes accounted for 59.3% of all cases. Post-infective is a poorly defined clinical entity often combined with idiopathic for analysis purposes. Asthma and COPD were frequently reported as the cause of bronchiectasis reflecting the overlap syndromes that have been previously shown to be associated with worse outcomes.^{28,29} It should be noted that unlike past studies in tertiary referral centres where all patients underwent standardised testing our results

	Exacerbations	Exacerbation leading to hospitalisation
UK		
Unadjusted	1 (ref)	1 (ref)
Adjusted*	1 (ref)	1 (ref)
Fully adjusted†	1 (ref)	1 (ref)
Northern and western Europe		
Unadjusted	0.76 (0.71–0.82)	0.94 (0.85–1.05)
Adjusted*	0.75 (0.70–0.81)	1.08 (0.96–1.21)
Fully adjusted†	0.72 (0.66–0.77)	1.05 (0.93–1.18)
Southern Europe		
Unadjusted	0.99 (0.92–1.06)	0.83 (0.74–0.94)
Adjusted*	1.06 (0.98–1.14)	1.04 (0.90–1.19)
Fully adjusted†	1.10 (1.02–1.19)	1.03 (0.90–1.19)
Central and eastern Europe		
Unadjusted	1.16 (1.04–1.28)	2.05 (1.79–2.36)
Adjusted*	1.02 (0.92–1.14)	1.61 (1.36–1.89)
Fully adjusted†	1.12 (1.01–1.25)	1.71 (1.44–2.02)

This analysis included data for 9978 patients who had at least 1 year of follow-up data: 652 patients from central and eastern Europe; 1831 patients from north and western Europe; 1838 patients from southern Europe; 5657 patients from the UK. Data are rate ratio (95% CI). Adjusted includes exposure and outcome only. COPD=chronic obstructive pulmonary disease. *Adjusted for age (continuous), sex (male or female), smoking (never, ex-smoker, current-smoker), *Pseudomonas aeruginosa* infection (yes or no), cystic dilation (yes or no), aetiology (categorical), FEV₁% predicted (categorical >80%, 50–79%, 30–49%, or 0–29%) asthma history (yes or no), COPD history (yes or no). †Adjusted for age, sex, smoking, *Pseudomonas* infection, cystic dilation, aetiology, FEV₁, asthma history, COPD history, inhaled corticosteroid use (yes or no), inhaled antibiotic use (yes or no), macrolide use (yes or no), hypertonic saline use (yes or no), regular chest physiotherapy (yes or no).

Table 4: Negative binomial models for the relationship between region and exacerbations during follow-up (n=9978 patients)

reflect the causes of bronchiectasis assigned by clinicians in real-life clinical practice.³⁰ Underdiagnosis of immunodeficiency, allergic bronchopulmonary aspergillosis, non-tuberculous mycobacterial infection, and PCD, among other underlying conditions, are well documented.^{31,32} The very high frequency of unidentified causes of bronchiectasis in Europe suggest the need for further research to optimise testing protocols as well as to develop new methods such as genomic sequencing to identify the cause in the idiopathic and post-infective subgroups.^{32,33}

The data from the registry regarding microbiology are fascinating and suggest important heterogeneity between countries. *P aeruginosa* was far more common in southern Europe whereas *H influenzae* was more common in the UK and northern and western Europe. The high rate of *P aeruginosa* and the remarkably low frequency of *H influenzae* in southern Europe is unlikely to reflect differences in patient characteristics, since severity, comorbidities and lung function were quite similar. Laboratory methods for detection of pathogens might vary between regions but this also seems an unlikely explanation for the differences observed. Environmental conditions as well as overall antibiotic

consumption across the population are different between northern and western and southern Europe. Studies using molecular methods have previously shown important geographical variation,^{34,35} and microbiome studies to date from southern Europe show a low frequency of the *Haemophilus* generally consistent with our findings.³⁶ Studies suggest organisms such as *P aeruginosa* are typically acquired from the environment and so differences in environment and climate are likely to be relevant.^{37,38} It is probable that these differences reflect true variation in the lung microbiome and are likely to have additional effect on the disease course and response to therapy.

Our data show a high burden of disease of bronchiectasis in Europe with a median of two exacerbations per patient per year. More than a third of patients across all regions were classified as having frequent exacerbators—defined as patients experiencing at least three exacerbations per year, a group with increased mortality, an increased rate of future hospital admissions and poor quality of life.²⁷ 26.4% of patients overall were hospitalised in the year before the study with an exacerbation leading to hospitalisation. Hospital admissions are therefore common in the bronchiectasis population and contribute to the very high economic burden of bronchiectasis on health-care systems.^{2,39} Bronchiectasis has traditionally been classified as an obstructive lung disease, but our data suggest that this is an oversimplification. The heterogeneity of lung function impairment in bronchiectasis has been previously described with air trapping and impaired gas transfer being common even in patients with preserved spirometry.⁴⁰ In our analysis which was limited to spirometry alone, 34.9% of patients had airflow obstruction whereas 31.2% had normal spirometry. PRISm is a relatively recent term used to describe patients with an FEV₁ less than 80% of predicted but without a FEV₁/forced vital capacity ratio of less than 0.7 (values less than 0.7 are suggestive of airflow obstruction).⁴¹ PRISm has been shown to be associated with respiratory symptoms and increased mortality in the general population and can be a precursor to airflow obstruction.⁴¹ We show here that nearly a quarter of patients with bronchiectasis meet the criteria for PRISm. Of note, we found that airflow obstruction including severe airflow obstruction was more common in patients from central and eastern Europe.

Across all analyses we found evidence of higher severity of disease including a high BSI, more hospitalisations, worse symptoms, and worse lung function in patients from central and eastern Europe. Despite this, patients from this region receive far fewer drug treatments than patients from other regions. We prospectively tested the hypothesis that these patients would have worse outcomes and showed that during follow-up in the registry patients from central and eastern Europe have more exacerbations and hospital admissions even after adjustment for multiple patient characteristics. These data have

important implications for care of patients in this region, where there have previously been few reports of bronchiectasis. One possible explanation for our findings is selection bias. Bronchiectasis is known to be underdiagnosed and it might be particularly underdiagnosed in some countries with less developed health-care systems. Therefore the registry might only be enrolling patients with very severe bronchiectasis in central and eastern Europe because less severe patients are not being diagnosed or referred to secondary care centres. Hospital admission data might be affected by the availability of primary care and home intravenous antibiotic services. Nevertheless, our data suggests that patients in this region are more likely to have post-infective disease and that such patients have lower lung function from early adulthood. It is therefore possible that the worse phenotype is related to more extensive lung damage acquired through early life infections or a failure to achieve maximal lung function, or combination of these circumstances.⁴² Our data suggest a different phenotype of patients in central and eastern Europe and an urgent need to provide patients access to evidence based therapies such as airway clearance and macrolides which have proven efficacy in bronchiectasis and are underutilised.⁴³ It would be important for future clinical trials to understand if the different phenotypes observed in different regions in our study translate into differences in treatment response. Our data do not, however, explain well documented differences in trial results in eastern Europe where low exacerbation rates have been encountered.^{16,17} Our data, suggest, if anything, that higher exacerbation rates should be expected in this region. This contradiction remains unexplained. Our data show inequality in access to treatment and outcomes across Europe, a continent with generally well developed health-care systems relative to the rest of the world. Such inequality is likely to be even greater globally and therefore the need to ensure access to evidence-based care is not limited to Europe.

Bronchiectasis is a disease without an established standard of care and without any licensed therapies.⁸ It is therefore not surprising that in the absence of a strong evidence base there is a high degree of variation in the use of different treatments. A striking finding of our analysis was that inhaled corticosteroids were used by more than 50% of patients with bronchiectasis in Europe and between a third and a half of all patients across the majority of countries included in the EMBARC cohort were using inhaled corticosteroids. According to the 2017 European Respiratory Society guidelines inhaled corticosteroids are only indicated in patients with a history of asthma or COPD.⁸ Our data suggest widespread use of inhaled corticosteroids in patients with bronchiectasis without documented COPD or asthma. Inappropriate inhaled corticosteroid use runs the risk of increasing respiratory infections through increasing pathogenic proteobacteria, and inhaled corticosteroids use has been

linked to an increase in pneumonia as well as non-tuberculous mycobacterial infection.⁴⁴ Conversely, recent data suggests that 20–30% of patients with bronchiectasis might have eosinophilic inflammation, a type of inflammation that responds to inhaled corticosteroid treatment.⁴⁵ Our data suggest the need for more clear guidance on the use of inhaled corticosteroids and research into whether biomarkers such as blood eosinophil counts can guide inhaled corticosteroids use.

This analysis has unique strengths including the very large sample size and detailed patient characterisation. It also has important limitations intrinsic to the observational nature of the study. We did not mandate aetiological testing or sputum testing and so results are inevitably dependent on physician practice in different regions. Recruitment between different countries was not balanced and in particular we observed high recruitment in the UK. The UK has a well developed clinical research infrastructure as illustrated during the COVID-19 pandemic⁴⁶ and this resulted in strong recruitment to the study. Studies found an overall prevalence of bronchiectasis of 566 per 100 000 in females in 2013 in the UK compared with 68 per 100 000 in females in Germany in 2013.⁴⁷ We believe it is unlikely this reflects true differences in prevalence and might reflect different methodologies of the studies, as well as differences in the awareness of the condition, and health-care organisational factors such as reimbursement.^{5,47} Nevertheless, despite small numbers of patients from some countries, patterns of severity and treatment practice were remarkably consistent between different countries in the same region suggesting the regional level analyses are valid.

In summary, we provide the largest and most detailed characterisation of bronchiectasis reported to date. Bronchiectasis is shown to be a heterogeneous disease across Europe with the causes, severity, microbiology, and treatment being highly dependent on the region and patient characteristics. EMBARC will be an important platform for exploring different aspects of bronchiectasis assessment and treatment in the future.

Contributors

JDC, EP, MLC, FCR, ADS, TW, FB, JSE, PCG, and SA conceived of and designed the study. JDC, EP, MLC, FCR, ADS, JSE, and SA conducted the study and were responsible for its management. All authors were involved in patient enrolment and data collection. Data analysis and interpretation was performed by JDC, EP, MLC, FCR, ADS, MV, PRB, CH, MRL, and SA. JDC, MLC, and SA had directly accessed and verified the data. The manuscript was drafted by JDC, MLC, and SA. All authors reviewed, contributed to, and approved the final version of the Article. The corresponding author had the final responsibility to submit for publication.

Declaration of interests

JC reports grants or contracts from Grifols; consulting fees from Antabio, AstraZeneca, Boehringer Ingelheim, Chiesi, Glaxosmithkline, Grifols, Insmad, Janssen, Novartis, Pfizer, and Zambon; and leadership or fiduciary roles as Chair of European Respiratory Society (ERS) Bronchiectasis Guideline Task Force, Chief Editor of *European Respiratory Journal*, and Chair of EMBARC Clinical Research Collaboration.

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Data sharing

Data from the European Bronchiectasis registry are available to collaborators through an application process. Contact info@bronchiectasis.eu for further information.

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