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Heterogeneous use of multiple breath washout in cystic fibrosis across age groups and European countries: an ECFSPR analysis

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ABSTRACT

Multiple breath washout (MBW) and its primary output, lung clearance index (LCI), sensitively measure ventilation inhomogeneity in cystic fibrosis (CF). This study aimed to characterize real-world MBW use in Europe through retrospective analysis of 2023 data from the European Cystic Fibrosis Society Patient Registry (ECFSPR).

We determined the proportions of people with (pwCF) with one MBW measurement in 2023 by age group, lung function, country and device used.

We analysed data from 39,986 non-transplanted paediatric and adult pwCF from 40 countries.

Overall, 10 % of pwCF had an MBW measurement in 2023. MBW was performed in 22 countries and in 12 % of pwCF in those countries. Austria had the highest overall MBW use (39 % of pwCF). The highest proportions of pwCF who had MBW were aged 6–11 years (23 %) and 12–17 years (23 %). MBW was mostly used in pwCF with normal (19 %) or mildly impaired (10 %) percent predicted forced expiratory volume in one second. The Eco Medics Exhalyzer® D N2 was the most commonly used device (83 %).

MBW is not yet routinely used in CF care in many European countries, presenting a window of opportunity to standardise MBW devices, software, and data quality control processes. This will ensure the accuracy and reliability of LCI measurements across different centres and devices, and facilitate MBW implementation in research and in care.

1. Introduction

In cystic fibrosis (CF) lung health declines throughout life due to damaging cycles of infection and inflammation, and normal aging [1]. Many adults with CF with "milder" genotypes and children with CF have "near-normal" spirometry [2]. Therefore, the use of more sensitive techniques can detect early lung disease and structural changes, helping predict health outcomes and aiding decision-making around early intervention [2].

The multiple breath washout (MBW) lung function test assesses ventilation inhomogeneity during tidal breathing [3]. Its primary output, lung clearance index (LCI), indicates small changes and impairments in lung function more sensitively than percent of predicted forced expiratory volume in 1 second ($ppFEV_1$) measured using spirometry [2,4]. MBW is thus useful in children with CF with near-normal lung function [5], especially those aged <6 years who struggle with the active cooperation required for spirometry [4,5]. Since cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies slow lung function decline, a sensitive measure such as MBW will help enable more accurate lung function monitoring, earlier detection of lung disease and treatment optimization [6,7].

LCI is already used as a standardised clinical trial outcome [7], and

MULTIPLE BREATH WASHOUT USE IN cystic fibrosis

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MBW has been implemented into clinical care in many European centres [8], with evidence of impact in paediatric treatment decision-making [6]. Recent real-world evidence from Denmark demonstrated significantly improved LCI in children after 12 months of elexacaftor/tezacaftor/ivacaftor treatment [9].

However, there is little evidence on MBW use in clinical practice across Europe. Therefore, we aimed to characterize MBW use in Europe in 2023 using real-world evidence from the ECFS Patient Registry (ECFSPR).

2. Methods

This retrospective analysis used ECFSPR data (extracted February 7, 2025) from people with CF (pwCF) who never had a transplant seen in 2023 in 40/43 ECFSPR countries (Belgium did not have data available for 2023, the UK does not collect information about MBW and Luxembourg declined participation). Since 2018, the ECFSPR annually records whether an individual had an MBW measurement, the MBW device used and the date and value of the lowest (best) $LCI_{2.5\ \%}$, defined as the number of lung volume turnovers required to reduce the concentration of an inert tracer gas to 2.5 % of its starting value.

2.1. Statistics

Descriptive data are presented, with categorical variables expressed as counts and percentages. Proportions of pwCF with MBW use are presented by 1) overall and by 2) age group, country and category of $ppFEV_1$ impairment (for pwCF aged ≥6 years with available $ppFEV_1$ in 2023) for countries with ≥1 pwCF who had an MBW measurement in 2023. Subgroup analyses were also presented by age group per country, where there were ≥20 pwCF in each age group. $ppFEV_1$ was calculated using Global Lung function Initiative (GLI) 2012 equations [10], using

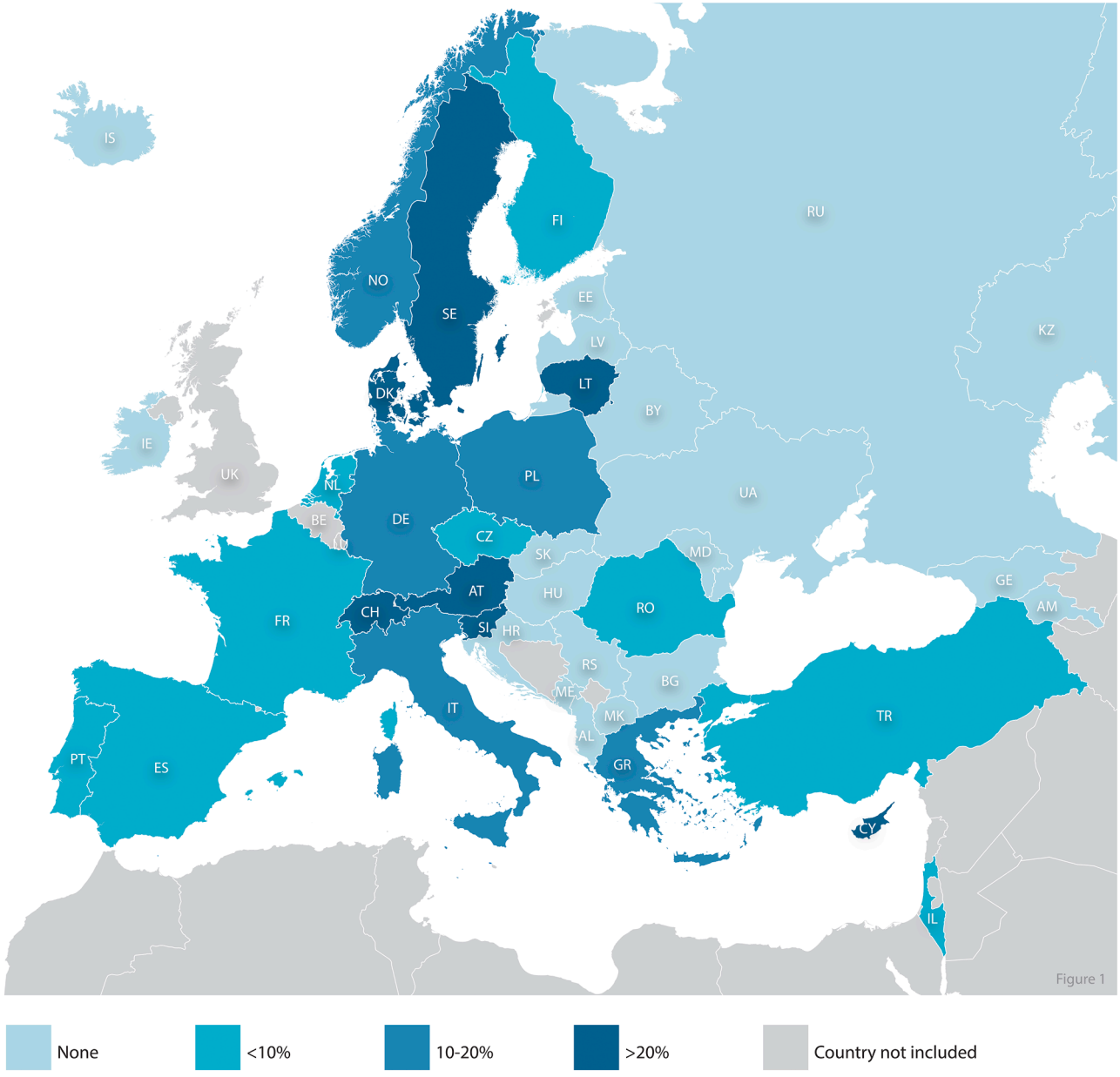

Fig. 1. Proportion of pwCF with an MBW measurement in 2023, by country.
Abbreviations: pwCF=people with cystic fibrosis; MBW=multiple breath washout.
Colour coding corresponds to the proportion of pwCF who had an MBW lung function assessment in 2023. Austria had the highest proportion of pwCF with an MBW measurement in 2023 (39 %).

the best measurement in 2023. ppFEV$_1$ categories were defined as normal (>90 %), or impairment that was mild (71-90 %), moderate (41-70 %) or severe impairment (≤40 %). We tested for differences between age groups and between FEV$_1$ severity categories using the chi-squared test. Data were analysed using SAS statistical software, version 9.4 (SAS Institute Inc., 2020).

2.2. Ethics

All participating ECFSPR national registries and individual centres have ethics approval and informed consent from participating pwCF, including permission to use data for future research. The ECFSPR Scientific and Steering Committees approved the study.

3. Results

Analysis of 39,986 pwCF showed MBW was performed in 22/40 countries in 2023 (Fig. 1). At the beginning of 2023 for these 39.986 patients, median age was 18 years (interquartile range 9-30) and 52 % were male. Overall, 10 % of pwCF across these 40 countries had an MBW measurement, ranging from 0-39 % per country. Countries where >20 % of pwCF had an MBW measurement were Austria (39 %), Cyprus (38 %), Slovenia (36 %), Sweden (36 %), Lithuania (33 %), Denmark (25 %) and Switzerland (25 %) (Table 1).

Among the 22 countries in which ≥1 pwCF had an MBW measurement in 2023, 12 % of pwCF had an MBW measurement.

MBW use differed significantly across age groups ($p<0.0001$) overall, and in each country with data ($p<0.0001$). The highest proportions of pwCF with an MBW measurement were in the age groups 6–11 years (23 %) and 12–17 years (23 %) (range, 0–100 % per country in both age groups) (Fig. 2). This was consistent across countries. Austria had the highest rate of MBW use in adult age groups (Table 1).

MBW use differed significantly across FEV$_1$ severity categories ($p<0.0001$). In countries that performed MBW in 2023, MBW was predominantly used in pwCF aged ≥6 with normal (19 %) or mildly impaired (10 %) ppFEV$_1$, and rarely in pwCF with moderate (4 %) or severe (2 %) ppFEV$_1$ (Table 2).

MBW was assessed using the Eco Medics Exhalyzer® D N_2 (83 % of pwCF), followed by the NDD EasyOne Pro® (5 %), other (2 %, e.g. Innocor®, Eco Medics Exhalyzer® D SF_6), with data missing/unknown corresponding to 10 % of pwCF.

4. Discussion

Our data reveal a heterogeneous pattern of MBW use across Europe and indicate that MBW is not yet routinely used in CF clinical care in most countries.

In 2023, MBW was used in clinical practice in 55 % of countries, most of which were high-income countries (World Bank 2023 categories). Overall, just 10 % of pwCF across the 40 ECFSPR countries included had an MBW measurement (rising to 12 % across countries with ≥1 pwCF with an MBW measurement in 2023). The ECFS standards for the care of pwCF do not specifically recommend LCI for lung-health monitoring, but note that MBW is increasingly used to detect early structural lung disease in children and in adults with mild lung disease and near-normal spirometry [11]. Indeed, we observed that MBW is most often used in pwCF aged 6-17 years and in pwCF with normal or mildly impaired ppFEV$_1$. In adults, and pwCF with more severe lung disease, MBW can take a long time to perform, contributing to the lower rates of use in these populations.

Comparison of LCI data is hampered by differences in MBW devices [12], software and algorithms [13,14], and quality-control processes [15,16]. In our study, MBW was mostly measured using the Exhalyzer® D (83 %). Standardized protocols and quality-control assessments are thus essential to ensure accurate and reliable LCI measurements across different centres and equipment. To define "healthy" LCI, the Global Lung Initiative (GLI) recently published reference equations for LCI based on data from 1431 healthy individuals across 8 mostly European and high-income countries [3].

Longitudinal multicentre and multinational ECFSPR data on MBW could help track disease progression and treatment response in pwCF, especially in 6–17-year-olds. To further standardise data, the ECFSPR will collect the software and version for the Exhalyzer® D used to calculate LCI from the 2024 dataset onwards. Interestingly, the device and inert tracer gas used appear not to significantly impact prediction equations [3], meaning that aggregated LCI data from multiple devices could potentially be analysed. While there is currently no standardised pan-European training or quality control for MBW in clinical care, the ECFS Clinical Trials Network (ECFS-CTN) LCI Central Core Facility [17] trains European operators to perform MBW for clinical trials, thereby promoting data quality at the centre level. ECFSPR data from LCI Core Facility certified centres could provide a useful MBW subset of quality-controlled LCI measurements for sensitivity analysis.

Computed tomography (CT) data are currently being added to ECFSPR. The combination of structural (CT) and functional (MBW) lung data in larger cohorts could offer insights into CF beyond that possible with spirometry data alone [18]. We also anticipate a growing use for MBW to monitor lung function in clinically "well" pwCF on CFTR modulator therapy.

Standardised, longitudinal, multinational ECFSPR data on MBW use,

Table 1
Proportion of pwCF with an MBW measurement in 2023, by age group and country.

	pwCF with ≥1 MBW measurement / pwCF in age group in country performing MBW (%)							
Country performing MBW	All ages	0–1 year	2–5 years	6–11 years	12–17 years	18–29 years	30–39 years	≥40 years
Austria	296/ 762 (39)	9/46 (20)	20/77 (26)	85/ 125 (68)	87/ 141 (62)	53/ 200 (27)	31/ 112 (28)	11/ 61 (18)
Denmark	135/ 536 (25)	1–5	>5	49/ 63 (78)	47/ 66 (71)	0/141	0/91	0/82
France	322/6491 (5)	0/340	37/516 (7)	127/887 (14)	141/1047 (13)	12/1769 (0.7)	5/1061 (0.5)	0/871
Germany	951/ 6802 (14)	27/ 365 (7)	111/ 647 (17)	291/ 991 (29)	252/ 940 (27)	173/ 1751 (10)	59/ 1141 (5)	38/ 967 (4)
Greece	79/ 614 (13)	0/32	1–5	22/ 78 (28)	24/ 105 (23)	28/ 208 (13)	1–5	0/64
Ireland	66/1265 (5)	0/49	1-5	27/182 (15)	29/202 (14)	>5	0/220	0/158
Italy	881/ 5829 (15)	0/211	33/ 445 (7)	205/ 859 (24)	183/ 805 (23)	274/ 1478 (19)	98/ 894 (11)	88/ 1137 (8)
Netherlands	123/1508 (8)	0/59	9/103 (9)	55/191 (29)	59/203 (29)	0/409	0/271	0/272
Norway	57/ 335 (17)	0/25	1–5	15/ 37 (41)	19/ 45 (42)	13/ 75 (17)	8/ 52 (15)	1-5
Poland	312/ 1566 (20)	0/103	63/ 218 (29)	127/ 357 (36)	122/ 351 (35)	0/372	0/117	0/48
Spain	93/2331 (4)	0/122	0/196	33/400 (8)	30/406 (7)	7/522 (1)	0/301	23/384 (6)
Sweden	250/702 (36)	6/ 26 (23)	19/ 60 (32)	70/ 91 (77)	100/ 114 (88)	26/ 164 (16)	20/ 119 (17)	9/128 (7)
Switzerland	225/ 919 (24)	0/37	24/ 76 (32)	99/ 150 (66)	93/ 143 (65)	6/244 (2)	1–5	1–5

Abbreviations: pwCF=people with cystic fibrosis; MBW=multiple breath washout.
Notes: This table presents the proportion of pwCF with an MBW measurement in 2023 in each group by country (for all countries with ≥1 pwCF with an MBW and where there were ≥20 pwCF in each age group). To protect data privacy, the number and % of pwCF with an MBW measurement is displayed in each cell only if >5 pwCF had an MBW. Otherwise data are displayed as 0, 1-5, with a further count in that subgroup presented as >5 to prevent back calculation.

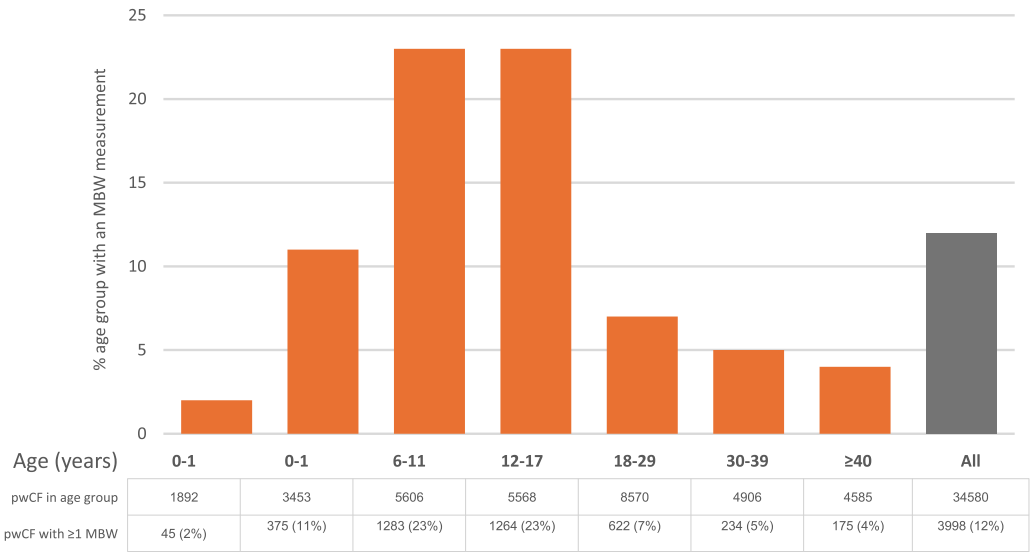

Fig.2. Proportion of pwCF with an MBW measurement in 2023, by age group.
Abbreviations: pwCF=people with cystic fibrosis; MBW=multiple breath washout.
Notes: this figure shows the proportion of pwCF with an MBW measurement in 2023 by age group and overall in countries with ≥1 pwCF with an MBW measurement (12 %).

Table 2
MBW proportions by category of lung function impairment measured by $ppFEV_1$.

Lung function (spirometry-derived)	Number of pwCF	pwCF with MBW n (%)
All pwCF aged ≥6 with available $ppFEV_1$ in 2023	28085	3636 (13)
Severe ($ppFEV_1$ ≤40 %)	1327	28 (2)
Moderate ($ppFEV_1$ 41-70 %)	5643	251 (4)
Mild ($ppFEV_1$ 71-90 %)	6849	704 (10)
Normal ($ppFEV_1$ >90 %)	14266	2653 (19)

Abbreviations: pwCF=people with cystic fibrosis; ppFEV1=percent predicted forced expiratory volume in one second; MBW=multiple breath washout.
Notes: This analysis was performed for pwCF aged ≥6 with available $ppFEV_1$ in countries with ≥1 pwCF with an MBW in 2023.

methodology (devices and software), and results will help build understanding of early and mild CF lung disease, including individual trajectories. Such evidence will support integration of MBW into clinical care to better monitor and guide treatment, especially for early CF lung disease.

5. Conclusion

In 2023 MBW was performed in 22 countries across ECFSPR and in 12 % of pwCF, most often in in children with CF aged 6-17 years and in adults with normal to near-normal FEV_1. This limited real world MBW use presents a window of opportunity to standardise MBW devices, software, and data quality control processes to increase the reliablity and use of MBW in research and in care.

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Author credit

AZ: Conceptualization, Data curation,Formal analysis, Writing- review & editing; **SG:** Writing-review & editing; **AL:** Conceptualization, Writing-review & editing; **PG:** Conceptualization, Writing-review & editing; **CS:** Writing-review & editing; **LN:** Conceptualization, Writing-review & editing.

Declaration of competing interest

AZ, PG, CS, AL: declare no conflicts of interest related to the data presented in this manuscript. I have not received any financial support, personal compensation, or other benefits from any commercial or non-commercial entities that could influence the content or conclusions of this work.SG: received fees as a consultant for Viatris. LN: received institutional study funding by Vertex Pharmaceuticals and the German Center of Lung Research, participated in the Trial Steering Committee for CF Storm, acted as the Medical lead of the German CF-registry and as Pharmacoepidemiology Study Director of the ECFSPR and received Medical writing support by Articulate Science.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jcf.2025.12.001.

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