German Cystic Fibrosis-Registry

Annual Report 2017

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Status: 2018-10-31

MUKOVISZIDOSE e.V.
Helfen. Forschen. Heilen.

Imprint

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Publisher:
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Langenbeckstraße 1, D-55131 Mainz
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Satz & Layout:
kitz.kommunikation GmbH Kreativagentur

Bibliographical data by the Deutschen Nationalbibliothek (German National Library):

ISBN 978-3-9818545-7-2

Preface

**PD Dr. med.
Lutz Nährlich**

Medical Director
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The German Cystic Fibrosis-Registry is an important source of information for assessing the health status of people with cystic fibrosis in Germany. The present collective report from year 2017 presents the data of 6106 people with cystic fibrosis from 91 outpatient clinics. The share of adult patients is 58.1%, and the median age is 20. A CFTR genotyping important in the era of mutation-specific therapies is available in 99.2% of all the cystic fibrosis patients included in the report. 93.3% of these patients are known to carry both mutations. 78% of the children and adolescents, and 70% of the adults, have a normal nutritional status. At the age of 16–17 years, 61% of the adolescents have an age-appropriate FEV1%predicted greater than 80%. Chronic *Pseudomonas aeruginosa* infection is found in 10.4% of the children and adolescents, and in 54.6% of the adults. 55% of the documented cystic fibrosis patients were treated with antibiotics for exacerbations, and 32% have a documented CF-relevant hospitalisation. 8.7% had undergone an inpatient rehabilitation measure.

The highlight of this collective report is the report on the impact of the newborn screening for cystic fibrosis introduced on 01 September 2016, and the expanded reporting of the lifetime.

› As a result of the screening, the number of newly diagnosed cases increased to 206, and the median age at diagnosis decreased to 0.17 years. As many as 52% of those newly diagnosed in the reporting year were diagnosed though the screening.

› For the first time, we present further important parameters for lifetime, median survival age, and life expectancy. The median survival age for the period 2012–2016 was 47.5 years. By comparison, the median survival age in the same period and calculated using the same method was 42.7 years in the USA, 47 years in the United Kingdom, and 53.3 years in Canada. The life expectancy of a person with cystic fibrosis born in Germany between 2012 and 2016 was 50 years.

All this would not have been possible without the trust you have placed in us. I would like to extend my sincere thanks to all the clinic teams and to the consenting people with cystic fibrosis who allow us to document and evaluate their data. My thanks also go to the AG Register, the company Axaris (Ms Jaumann, Mr Müller, Mr Volk) and the new data management team of the Interdisciplinary Centre for Clinical Trials (IZKS) of Mainz University Medical Centre (Ms Wosniok, Ms Wollscheid, Mr Kronfeld, Mr Ruckes, Mr Engelmann). My special thanks go to Mr Burkhart from the Cystic Fibrosis Institute for his tireless efforts in project management.

Please keep supporting the Registry.

Gießen, November 2018
PD Dr. med. Lutz Nährlich

Collective description

For the reporting year 2017, progressive data records of 6106 patients are included into the evaluations. These patients have either signed a current informed consent form or had died before a new consent could be obtained. Patients who received a lung transplant in 2017 or earlier are excluded from the lung function assessments. Also excluded are patients under 6 years of age and patients who had no lung function test done. In total, 4905 records were thus available for assessment.

Overall, 85 values (1.4%) are missing for assessment of the nutritional status. The data on complications are missing in 50 patients (0.8%). A total of 174 values (3%) are missing for the assessment of pulmonary infections.

The progressive data records are collected once a year in the so-called level-1 clinics and recorded as "health status" for the entire calendar year or aggregated from the visit-related records of the so-called level-2 clinics, respectively. In the case of patients older than 6 years with a lung function test, the time of examination with the best FEV1% predicted and the corresponding body measurements are selected as the examination date in year 2017. In patients without a FEV1 value and in children younger than 6 years, the latest available body measurements are used in the reporting year. A complication at least once a year and/or a long-term therapy, microbiological evidence or a chronic infection determine the manifestation for the entire reporting year. If there are history records for a patient from several clinics, they are likewise aggregated in accordance with the above rules into a record for the collective report.

The mortality analyses include all the patients who died in the respective reporting year, irrespective of whether or not their history records are available. However, it excludes patients who had withdrawn their consent before death. The age of the patients was calculated in completed years for patients not reported as deceased at the end of the respective reporting year. For patients who died in the reporting year, the age at the time of death was calculated in completed years. In the case of deceased persons, for whom no date of death was documented, the age in completed years was calculated at the end of the reporting year.

Lung function was calculated using the reference values according to Wang et al. (Pediatr Pulmonol 1993; 15:793) for boys aged between 6–18 years and girls aged 6–15 years, and according to Hankinson et al. (Am Respir Crit Care Med 1999; 155: 179) for men older than 18 years and women older than 15 years. In addition, lung function was calculated and reported using the Global Lung Function Initiative reference (Quanjer et al; Eur RespirJ 2012; 40:1324).

For the Body Mass index (BMI), the reference values according to the KiGGS study (Robert Koch Institute: reference percentiles for anthropometric measures and blood pressure from the study on the health of children and adolescents (KiGGS), Berlin: RKI-Hausdruckerei, 2013) were used; for babies younger than 4 months, the reference values according to Kromeyer-Hauschild (Monatsschr Kinderheilkd 2001, 149:807) were used.

Contents

Map of participating CF sites within Germany in 2017

Fig. 1: Map of the participating CF sites within Germany in 2017

The map shows all 91 CF sites participating in the Register in 2017. Please report to us if your CF sites is not represented: register@muko.info. The CF site in Innsbruck is participating in the quality assurance measures for the Mukoviszidose-Registers (Cystic Fibrosis Register). The data thus collected is not taken into consideration in this evaluation.

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Brief overview

	2015	2016	2017
Data status	2016-10-28	2017-09-11	2018-09-18
Participating CF sites	90	92	91
Participating patients with follow-up data	5331	5720	6106
Age in year; median	20	20	20
Proportion of adults (≥ 18 years); %	56.5	56.8	58.1
Male patients in %	51.8	51.9	52.0
New diagnoses[1]	140	162	206
Age for new diagnoses in years; Median[1]	0.62	0.5	0.17
of these, diagnosis through new-born screening	22.4	22.8	51,9
Cases of death: number	80	63	48
Cases of death: % of all patients[2]	1.5	1.1	0.8
Age of death in median years;	32	33	32
(25.-75. P)	(24-38)	(23-41)	(23-39)
Transplantations[1]	28	40	37
of these, lung transplantations	25	36	32
of these, liver transplantations	5	2	5

Table 1: Brief overview of patients with follow-up data, valid informed consent form and CF diagnosis in the reporting year in Germany 2017

[1]The figure refers to patients diagnosed or transplanted in the year under review.
[2]This figure includes deceased patients without follow-up data in the reporting year.

Age structure

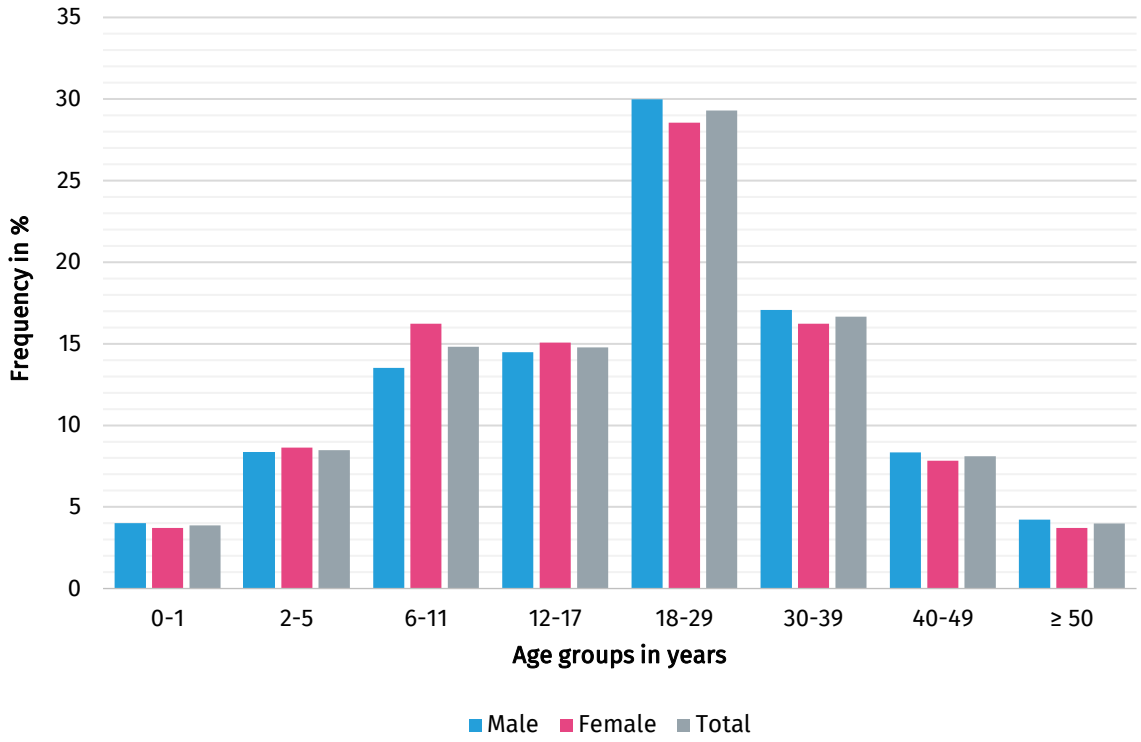

Fig. 2: Age distribution of those suffering from CF in 2017

	Male	Female	Total
Number	3174	2932	6106
Mean value [years]	22.3	21.5	21.9
Median [years]	21	20	20
Minimum [years]	0	0	0
Maximum [years]	79	75	79
Perzentil 25 [years]	11	10	11
Perzentil 75 [years]	32	31	31
Number < 18 years	1281	1280	2561
Number ≥ 18 years	1893	1652	3545

Table 2: Age distribution of those suffering from CF in 2017

03

Age structure

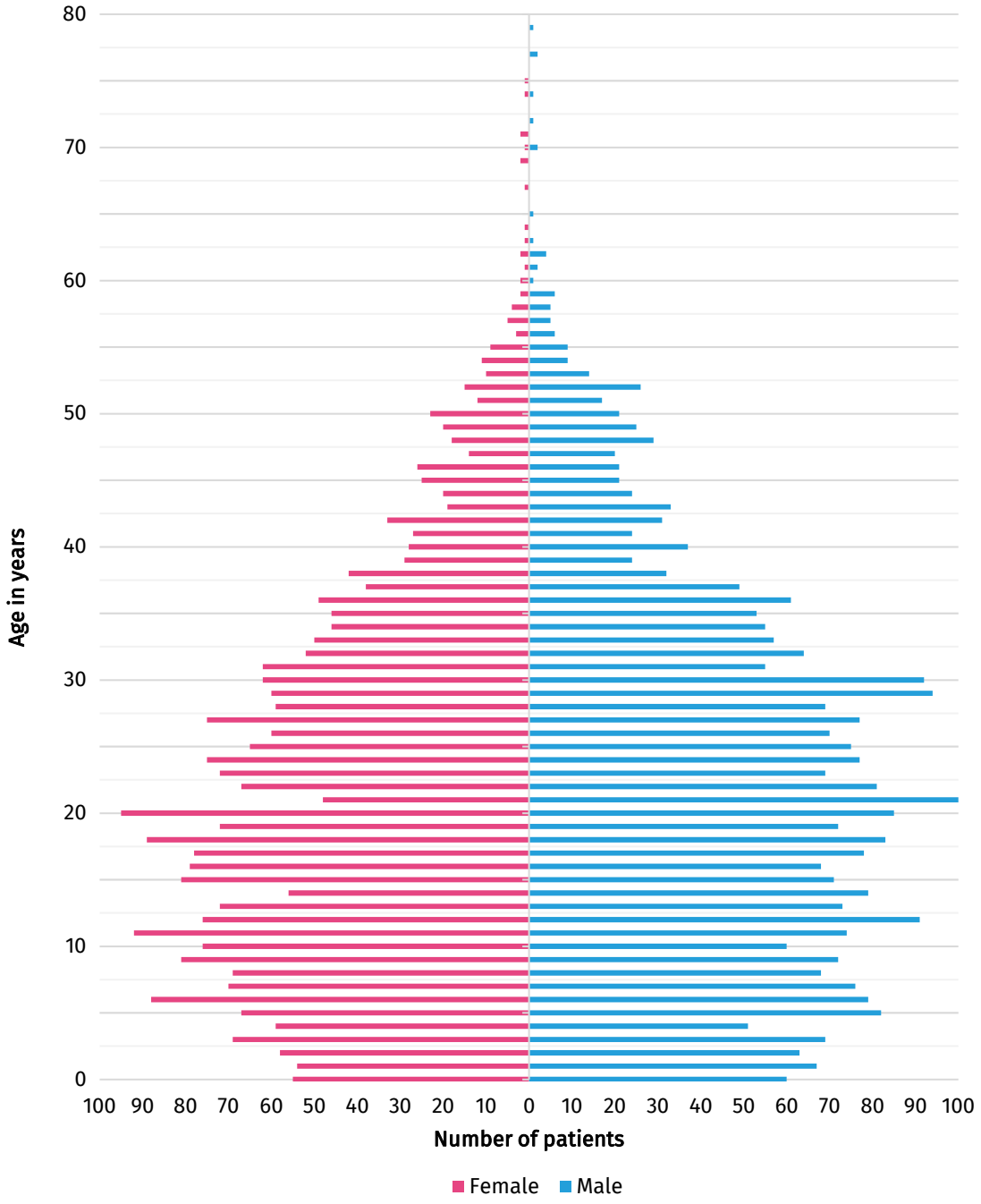

Fig. 3: Age pyramid of CF patients in 2017

CF diagnosis

4a. Diagnosis in 2017

In 2017, 206 patients were newly diagnosed, of 194 patients, follow-up data are available. The age distribution of the diagnosed patients is shown in the following tables:

	Mean value	Median	Minimum	Maximum	25.-75.P
Age in years	4.7	0.2	0.0	65.1	0.1-1.9

Table 3: Age of diagnosed patients at the time of diagnosis in 2017

Newborn screening was performed in 107 (51.9%) of newly diagnosed cystic fibrosis patients in 2017. 28 patients had a meconium ileus (13.6% of all patients diagnosed in 2017).

	Mean value	Median	25.-75.P
Age in days	34.2	25	14-39

Table 4: Age at diagnosis in patients newly diagnosed via newborn screening 2017

04

CF diagnosis

4a. Diagnosis in 2017

Age on diagnosis	Frequency	Percent	Accumulated percentages
0-3 month	119	58	58
4-6 month	15	7	65
7-11 month	8	4	69
1 year	13	6	75
2-5 years	20	10	85
6-11 years	7	3	88
12-17 years	7	3	92
≥ 18 years	17	8	100
Total	206	100	

Table 5: Age of diagnosed patients at time of diagnosis in 2017

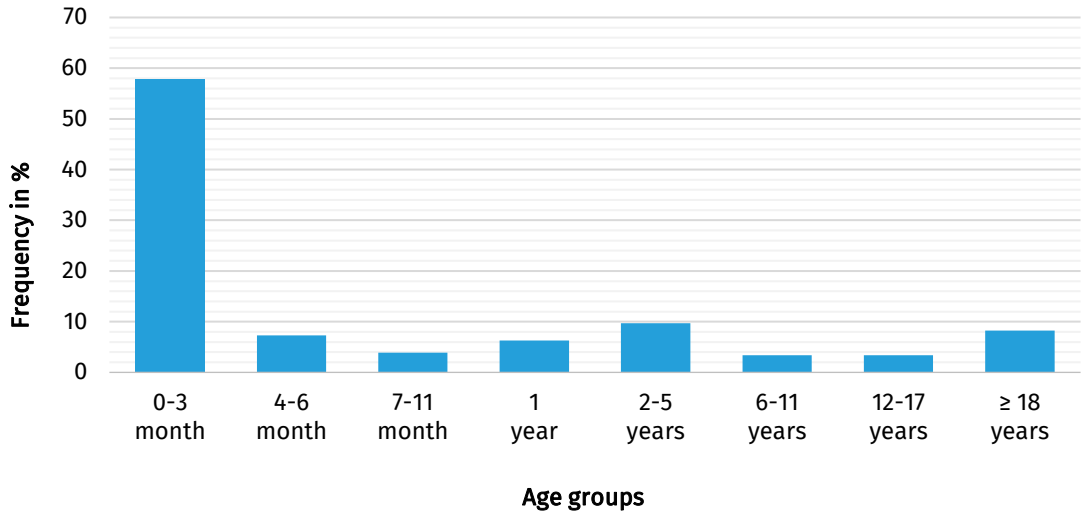

Fig. 4: Age-related frequencies in % of the diagnosed patients in 2017

CF diagnosis

4b. Age at time of diagnosis

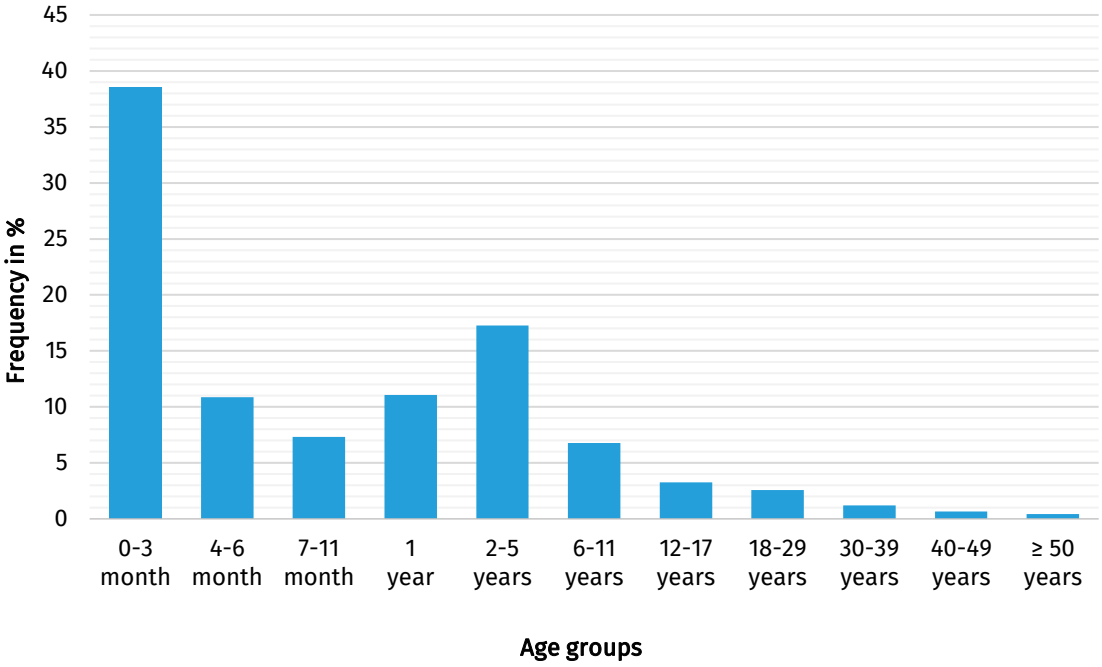

Fig.5: Age-related frequencies in % age on diagnosis – all patients Status 2017

Age on diagnosis	Frequency	Percent	Accumulated percentages
0-3 Monate	2252	38.5	38.5
4-6 Monate	636	10.9	49.4
7-11 Monate	427	7.3	56.7
1 year	647	11.1	67.8
2-5 years	1010	17.3	85.1
6-11 years	397	6.8	91.9
12-17 years	190	3.3	95.1
18-29 years	150	2.6	97.7
30-39 years	71	1.2	98.9
40-49 years	39	0.7	99.6
≥ 50 years	26	0.4	100.0
unknown	261		

Table 6: Age on diagnosis - all patients Status 2017

04

CF diagnosis

4c. Genotyping

Genotyping is available for 6055 (99.3%) of all patients.

Mutation combinations	Frequency	Percent
F508del homozygous	2831	46.8
F508del heterozygous: Secound mutation identified	2134	35.2
F508del heterozygous: No secound mutation identified	274	4.5
No verification of F508del: Both mutations identified	682	11.3
No verification of F508del: Only one mutation identified	69	1.1
No verification of F508del: No mutationen identified	65	1.1
Total	6055	100.0

Table 7: Mutation combinations 2017

The frequencies for the individual alleles are presented below, whereby only those with an absolute frequency of at least 50 are to be individually presented:

Allel	Number	Percent
F508del(p.Phe508del,c.1521_1523delCTT)	8070	66.7
N1303K (p.Asn1303Lys ,c.3909C>G)	244	2.0
G542X(p.Gly542X,c.1624G>T)	236	2.0
R553X(p.Arg553X,c.1657C>T)	225	1.9
G551D(p.Gly551Asp,c.1652G>A)	208	1.7
R347P(p.Arg347Pro,c.1040G>C)	171	1.4
CFTRdele2,3(p.Ser18ArgfsX16,c.54-5940_273+10250del21kb)	168	1.4
3849+10kbC->T(No protein name,c.3717+12191C>T)	126	1.0
1717-1G->A (No protein name,c.1585-1G>A)	104	0.9
W1282X (p.Trp1282X ,c.3846G>A)	85	0.7
2789+5G->A (No protein name,c.2657+5G>A)	83	0.7
2183AA->G(p.Lys684SerfsX38 ,c.2051_2052delAAinsG)	78	0.6
3272-26A->G(No protein name,c.3140-26A>G)	54	0.5
R117H(p.Arg117His,c.350G>A)	52	0.4
Other mutation	1733	14.3
Unknown and/or not identified	465	3.8
Total	12102	100.0

Table 8: CFTR-Genotyping 2017

Nutritional status

5a. Nutritional status for children and adolescents under 18 years

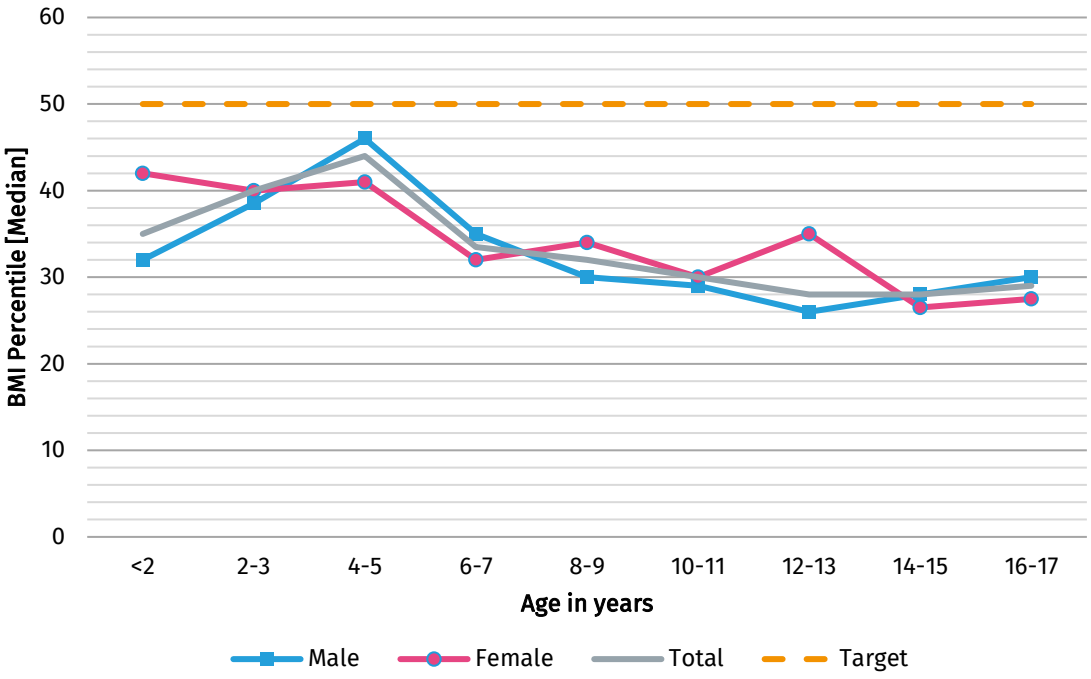

Fig. 6: Nutritional status for children and adolescents under 18 years in 2017

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
<2	220	35.0	11.5-67.5	117	32.0	11.0-68.0	103	42.0	12.0-67.0
2-3	263	40.0	14.0-66.0	136	38.5	15.0-66.0	127	40.0	14.0-64.0
4-5	287	44.0	21.0-67.0	147	46.0	20.0-69.0	140	41.0	22.0-64.5
6-7	324	33.5	15.0-58.5	157	35.0	18.0-61.0	167	32.0	12.0-57.0
8-9	280	32.0	17.0-55.5	133	30.0	19.0-56.0	147	34.0	17.0-53.0
10-11	312	30.0	12.0-52.5	147	29.0	10.0-56.0	165	30.0	14.0-49.0
12-13	305	28.0	13.0-53.0	164	26.0	12.5-44.0	141	35.0	13.0-60.0
14-15	289	28.0	10.0-50.0	145	28.0	11.0-50.0	144	26.5	9.5-49.5
16-17	341	29.0	10.0-52.0	171	30.0	9.0-54.0	170	27.5	11.0-51.0
Total	2621	33.00	13.0-57.0	1317	32.0	13.0-58.0	1304	33.0	14.0-56.0

Table 9: BMI percentile for children and adolescents under 18 years 2017 (Reference: KIGSS study or 0-3 months old, Kromeyer-Hauschild)

05

Nutritional status

5a. Nutritional status for children and adolescents under 18 years

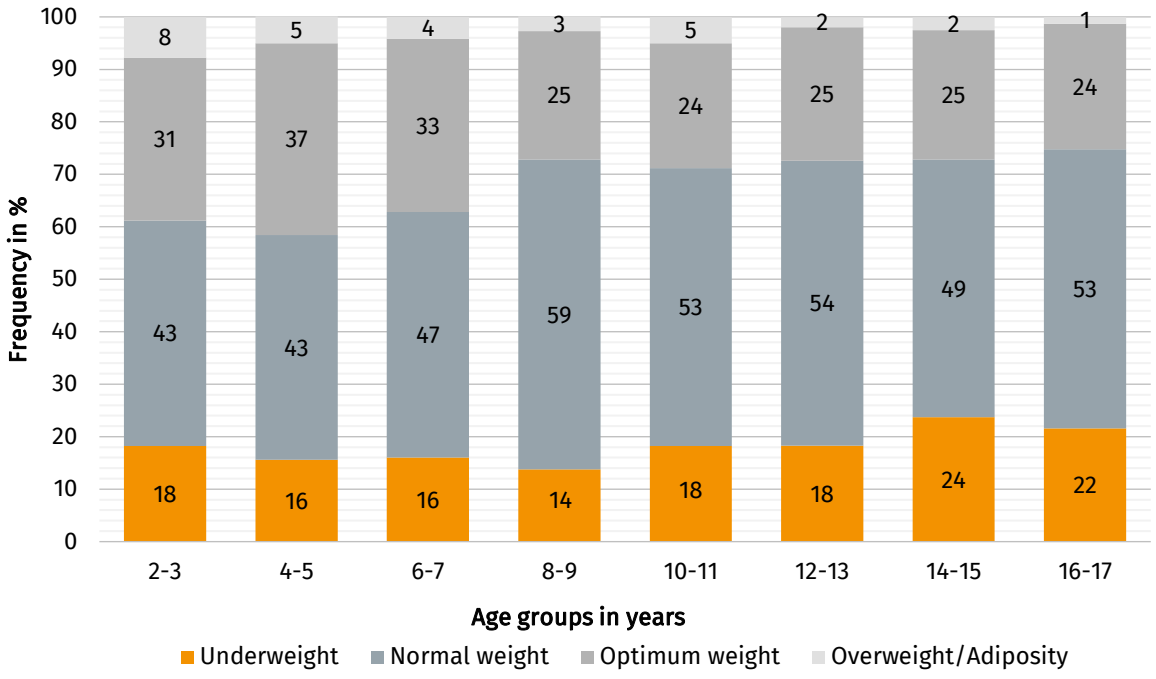

Figure 7: Nutritional status in % of children and adolescents under 18 years of age acc. BMI percentiles KIGGS 2017

Underweight: BMI percentile < 10; Normal weight: BMI percentile 10-49; Optimum weight: BMI percentile 50-89; Overweight/Adiposity: BMI percentile ≥ 90

	Male	Female	Total
Underweight	18.6	17.8	18.2
Normal weight	49.7	51.1	50.4
Optimum weight	28.2	27.2	27.7
Overweight/Adiposity	3.6	3.9	3.7

Table 10: Nutritional status in % of children and adolescents under 18 years of age acc. BMI percentiles KIGGS 2017

Underweight: BMI percentile < 10; Normal weight: BMI percentile 10-49; Optimum weight: BMI percentile 50-89; Overweight/Adiposity: BMI percentile ≥ 90

Nutritional status

5b. Nutritional status for adults 18 years and older

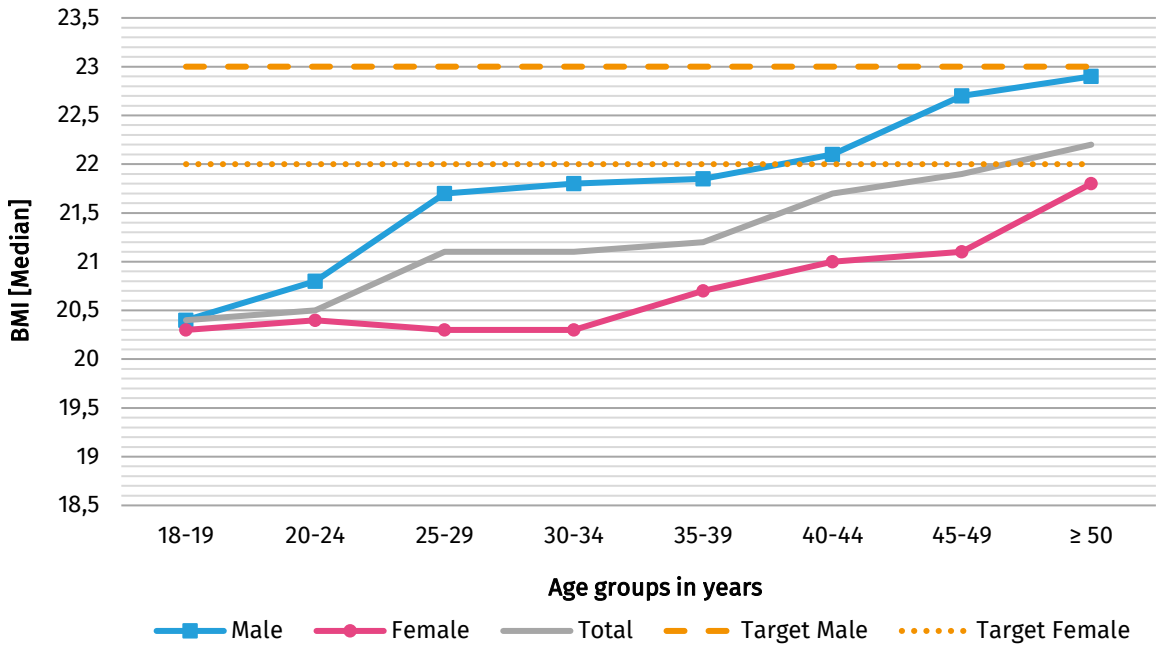

Figure 8: Nutritional status of adults 18 years and older 2017

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
18-19	304	20.4	18.7-22.3	139	20.4	18.6-22.4	165	20.3	18.8-22.2
20-24	740	20.5	18.9-22.6	403	20.8	19.0-23.0	337	20.4	18.7-22.2
25-29	705	21.1	19.3-23.3	390	21.7	19.8-23.9	315	20.3	18.8-22.5
30-34	566	21.1	19.1-23.4	305	21.8	19.6-24.2	261	20.3	18.8-22.3
35-39	401	21.2	19.3-23.4	210	21.9	19.9-24.5	191	20.7	19.0-22.6
40-44	255	21.7	20.0-23.7	135	22.1	20.6-24.2	120	21.0	19.0-23.0
45-49	214	21.9	19.9-24.0	115	22.7	20.5-24.6	99	21.1	19.2-23.4
≥ 50	215	22.2	20.1-24.6	117	22.9	20.7-24.8	98	21.8	19.5-24.1
Total	3400	21.1	19.2-23.3	1814	21.6	19.6-24.0	1586	20.5	18.9-22.6

Table 11: BMI of adults 18 years and older 2017

05

Nutritional status

5b. Nutritional status for adults from 18 years and older

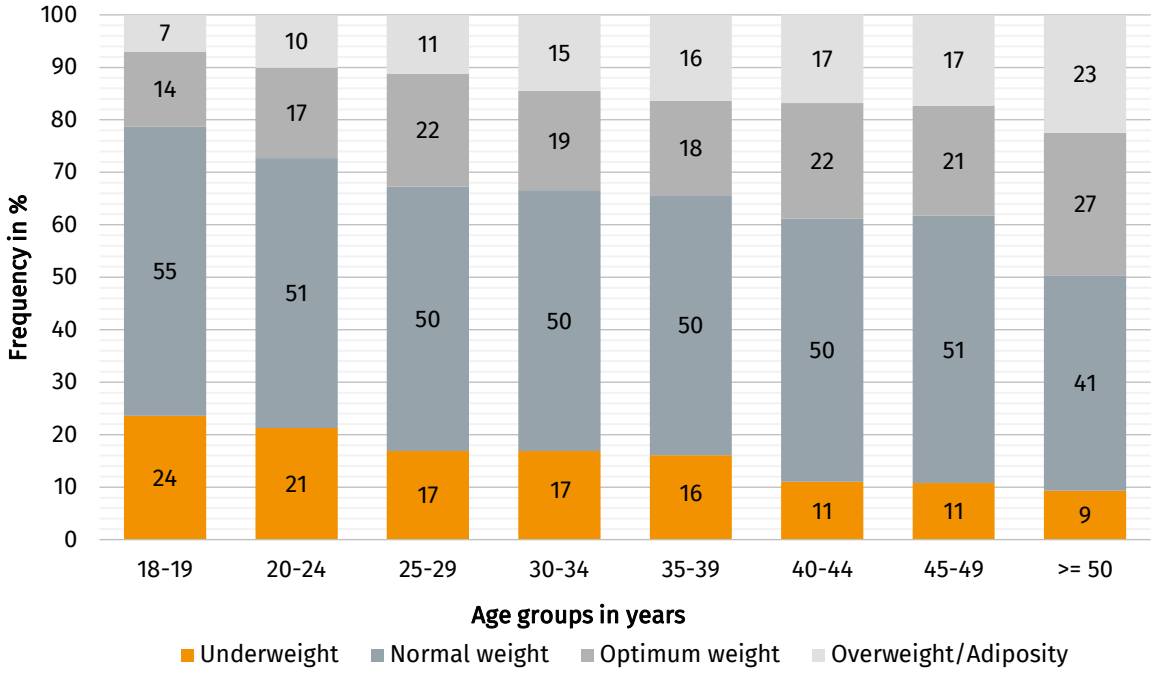

Figure 9: Nutrition status in % of adults 18 years and older 2017

Underweight: BMI < 18.5 kg/qm; Normal weight: Men: BMI 18.5 kg/qm -22.9kg/qm; Women: BMI 19.0-21.9 kg/sqm;
Optimal weight: BMI men 23.0 kg/qm-24.9 kg/qm, BMI women 22.0-24.9 kg/qm; Overweight/Adiposity: BMI ≥ 25 kg/qm

BMI	Male	Female	Total
Underweight	14.2	20.2	17.0
Normal weight	51.9	48.3	50.2
Optimum weight	17.6	21.5	19.5
Overweight/Adiposity	16.2	10.0	13.3

Table 12: Nutrition status in % of adults 18 years and older 2017

Underweight: BMI < 18.5 kg/qm; Normal weight: Men: BMI 18.5 kg/qm -22.9kg/qm; Women: BMI 19.0-21.9 kg/sqm;
Optimal weight: BMI men 23.0 kg/qm-24.9 kg/qm, BMI women 22.0-24.9 kg/qm; Overweight/Adiposity: BMI ≥ 25 kg/qm

Lung function FEV1%

6a. FEV1% acc. Wang & Hankinson (without lung transplant)

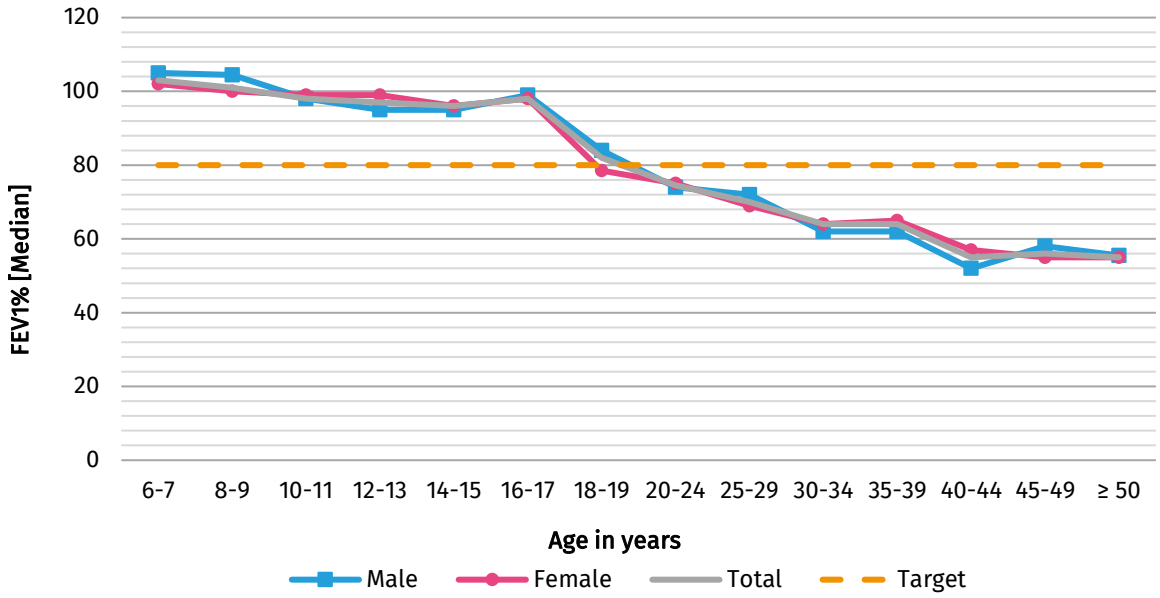

Figure 10: FEV1% value acc. Wang and Hankinson 2017

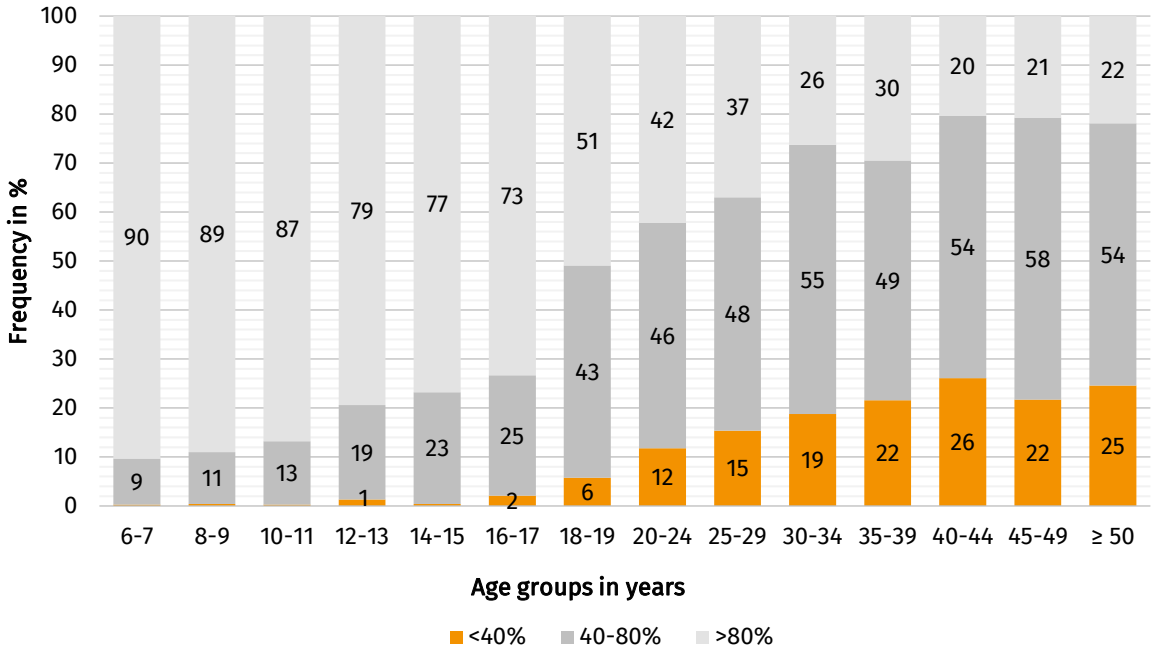

Figure 11: Age-related frequencies of severity of FEV1% (categories <40%, 40-80%, >80%) acc. Wang and Hankinson 2017

06

Lung function FEV1%

6a. FEV1% acc. Wang & Hankinson (without lung transplant)

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
6-7	309	103	92-115	149	105	92-116	160	102	93-114
8-9	274	101	91-113	128	105	93-115	146	100	90-112
10-11	310	98	87-108	146	98	87-107	164	99	88-109
12-13	301	97	84-105	161	95	83-103	140	99	88-107
14-15	285	96	83-107	144	95	85-106	141	96	76-109
16-17	334	98	78-111	167	99	78-111	167	98	77-111
18-19	291	82	64-98	135	84	70-100	156	79	61-95
20-24	704	75	54-94	387	74	52-94	317	75	55-93
25-29	651	70	50-89	366	72	54-89	285	69	48-88
30-34	501	64	44-82	274	62	43-84	227	64	47-80
35-39	348	64	43-84	190	62	39-85	158	65	48-83
40-44	226	55	39-76	121	52	39-75	105	57	40-76
45-49	184	56	43-78	98	58	42-81	86	55	45-73
≥ 50	187	55	40-78	100	56	37-80	87	55	42-77
Total	4905	82	57-100	2566	82	57-100	2339	82	58-101

Table 13: FEV1% value acc. Wang and Hankinson 2017

Lung function FEV1%

6b. FEV1% acc. GLI (without lung transplant)

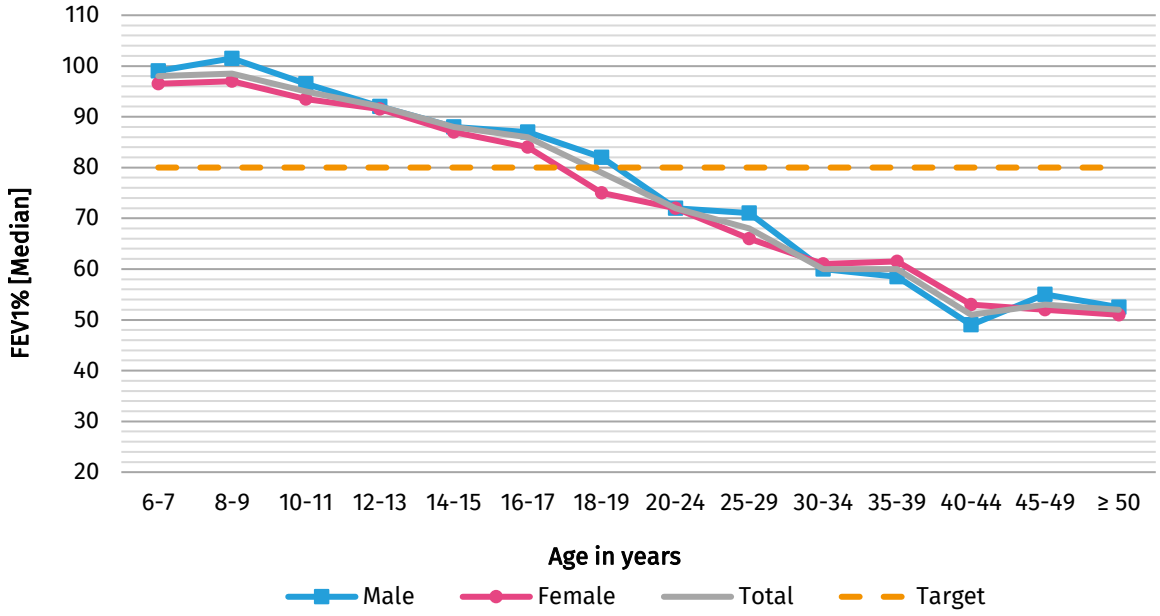

Figure 12: FEV1% value acc. Global Lung Initiative 2017

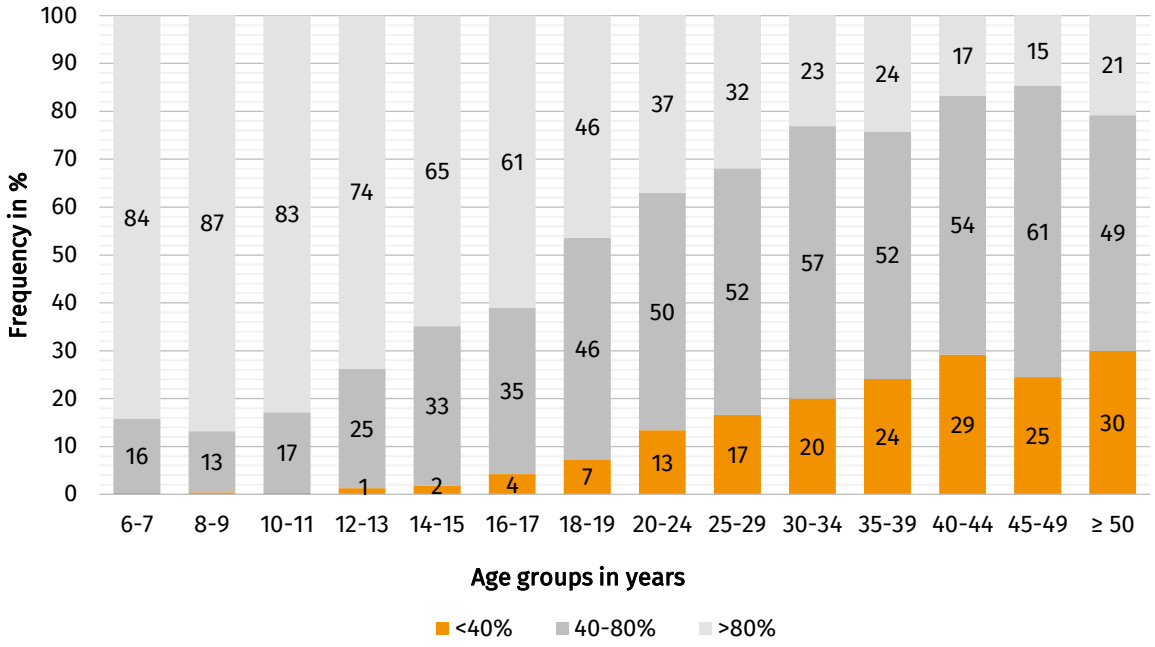

Figure 13: Age-related frequencies of severity of FEV1% (categories <40%, 40-80%, >80%) acc. Global Lung Initiative 2017

06

Lung function FEV1%

6b. FEV1% acc. GLI (without lung transplant)

	All			Male			Female		
Age in years	N	Median	25.-75. P	N	Median	25.-75. P	N	Median	25.-75. P
6-7	309	98	87-108	149	99	86-109	160	97	88-107
8-9	274	99	89-109	128	102	91-111	146	97	87-108
10-11	310	95	85-104	146	97	87-105	164	94	83-104
12-13	301	92	79-100	161	92	79-101	140	92	81-100
14-15	285	88	74-99	144	88	77-100	141	87	66-96
16-17	334	86	69-96	167	87	70-97	167	84	67-94
18-19	291	79	62-93	135	82	68-95	156	75	58-91
20-24	704	72	52-90	387	72	50-89	317	72	53-90
25-29	651	68	48-86	366	71	52-87	285	66	46-84
30-34	501	60	42-79	274	60	42-80	227	61	45-76
35-39	348	60	41-80	190	59	37-81	158	62	45-78
40-44	226	51	37-72	121	49	37-71	105	53	38-72
45-49	184	53	40-74	98	55	39-76	86	52	42-68
≥ 50	187	52	37-73	100	52.5	36-76	87	51	41-71
Total	4905	78	54-95	2566	78	54-95	2339	78	55-94

Table 14: FEV1% value acc. Global Lung Initiative 2017

Lung infections

7a. Annual verification at least once (without lung transplant)

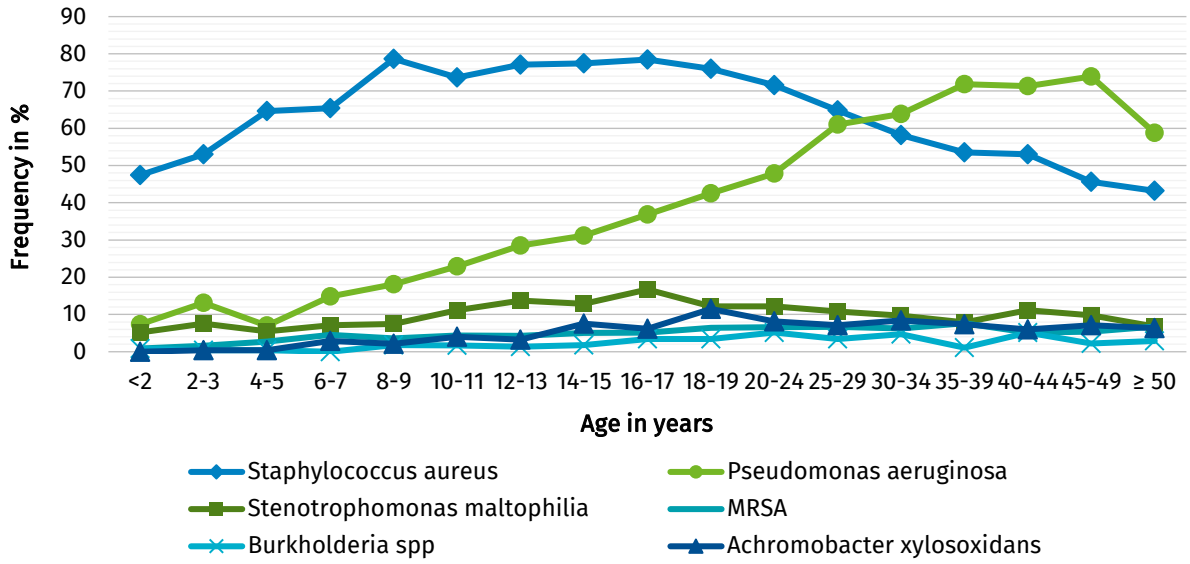

Figure 14: Age-related frequency of patients with bacterial detection in % with microbiological examination 2017

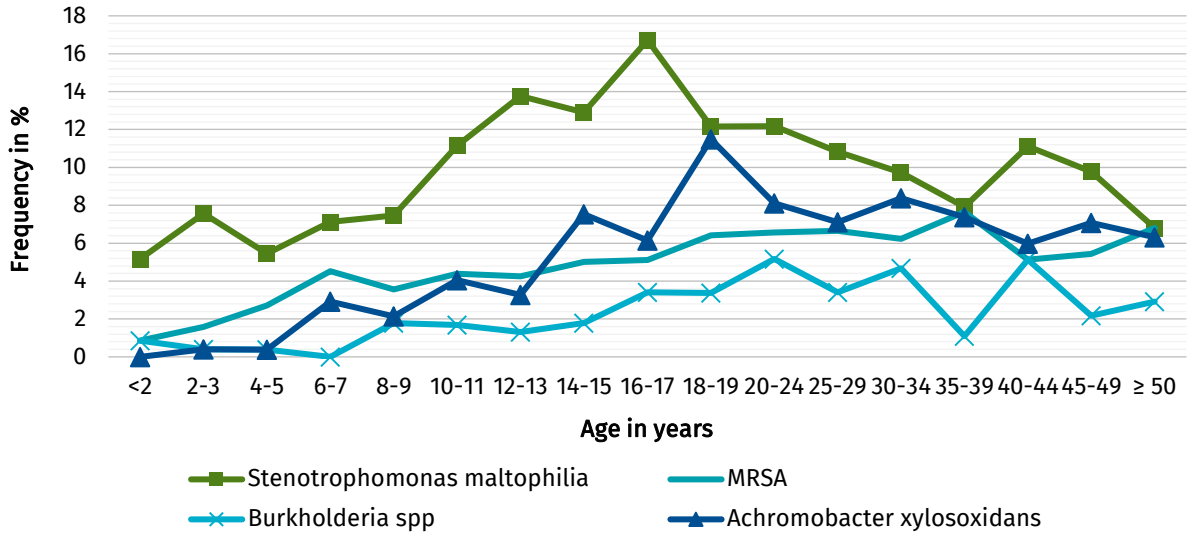

Figure 15: Age-related frequency of patients with bacterial detection in % with microbiological examination without Pseudomonas aeruginosa and Staphylococcus aureus 2017

07

Lung infections

7a. Annual verification at least once (without lung transplant)

Age in years	Staph. Aureus	MRSA	Pseudomonas aeruginosa	Burkholderia spp	Stenotroph-omonas maltophilia	Achromobacter xylosoxidans
<2	47.4	0.9	7.3	0.9	5.2	0.0
2-3	53.0	1.6	13.2	0.4	7.6	0.4
4-5	64.6	2.7	7.0	0.4	5.5	0.4
6-7	65.4	4.5	14.9	0.0	7.1	2.9
8-9	78.7	3.6	18.2	1.8	7.5	2.1
10-11	73.7	4.4	23.0	1.7	11.2	4.1
12-13	77.1	4.3	28.5	1.3	13.8	3.3
14-15	77.4	5.0	31.2	1.8	12.9	7.5
16-17	78.5	5.1	36.9	3.4	16.7	6.1
18-19	76.0	6.4	42.6	3.4	12.2	11.5
20-24	71.6	6.6	47.8	5.2	12.2	8.1
25-29	64.8	6.7	61.1	3.4	10.8	7.1
30-34	58.2	6.2	63.8	4.7	9.7	8.4
35-39	53.6	7.7	71.9	1.1	7.9	7.4
40-44	53.0	5.1	71.4	5.1	11.1	6.0
45-49	45.7	5.4	73.9	2.2	9.8	7.1
≥ 50	43.2	6.8	58.7	2.9	6.8	6.3
Total	64.9	5.2	42.2	2.7	10.2	5.8
<18	69.2	3.7	20.6	1.3	9.9	3.1
≥ 18	61.6	6.5	59.4	3.8	10.4	7.8

Table 15: Frequency of patients with bacteria detection in % with microbiological examination 2017

Lung infections

7b. Chronic lung infection (without lung transplant)

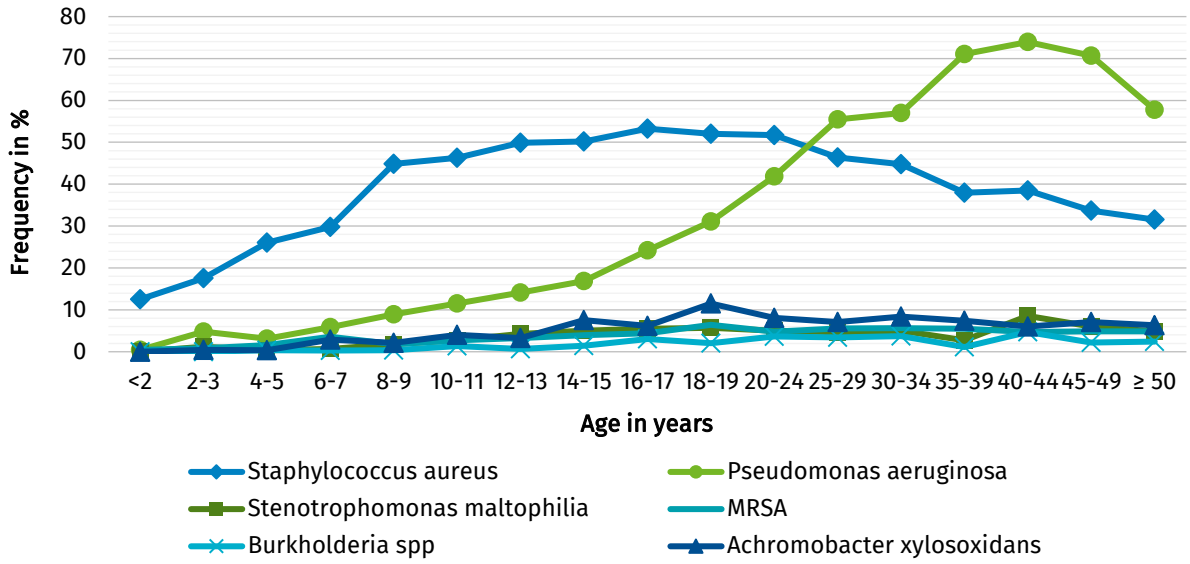

Figure 16: Age-related frequency in % of chronic lung infections 2017

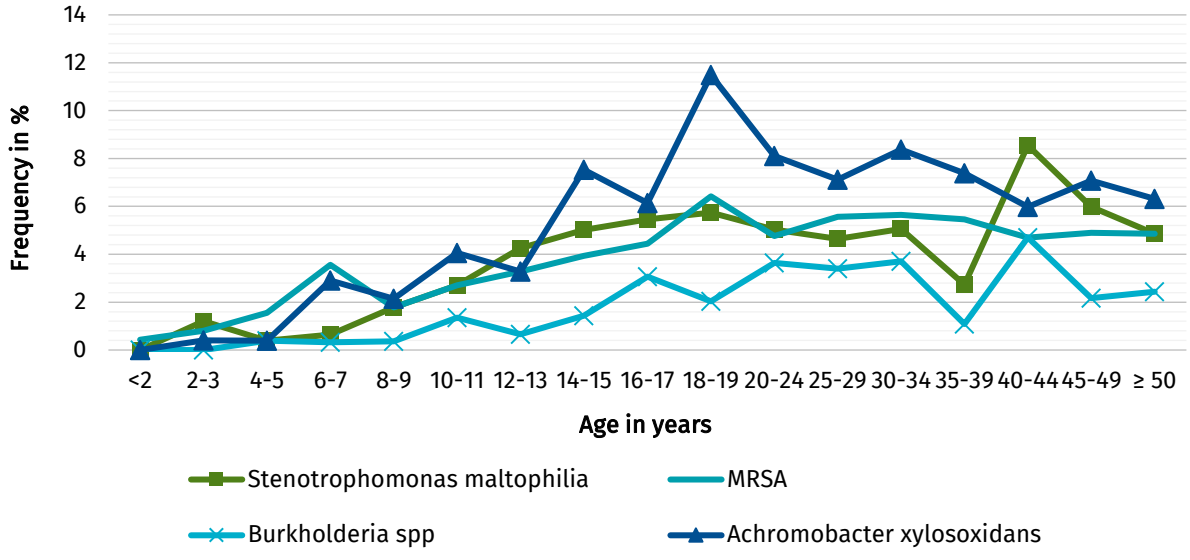

Figure 17: Age-related frequency in % of chronic lung infections without Pseudomonas aeruginosa and Staphylococcus aureus 2017

07

Lung infections

7b. Chronic lung infection (without lung transplant)

Age in years	Staph. Aureus	MRSA	Pseudomonas aeruginosa	Burkholderia spp	Stenotroph-omonas maltophilia	Achromobacter xylosoxidans
<2	12.5	0.4	0.4	0.0	0.0	0.0
2-3	17.5	0.8	4.8	0.0	1.2	0.0
4-5	26.1	1.6	3.1	0.4	0.4	0.0
6-7	29.8	3.6	5.8	0.3	0.7	1.6
8-9	44.8	1.8	8.9	0.4	1.8	0.0
10-11	46.3	2.7	11.5	1.4	2.7	1.7
12-13	49.8	3.3	14.1	0.7	4.3	1.6
14-15	50.2	3.9	16.9	1.4	5.0	3.6
16-17	53.2	4.4	24.2	3.1	5.5	2.7
18-19	52.0	6.4	31.1	2.0	5.7	6.4
20-24	51.8	4.8	41.8	3.6	5.0	4.6
25-29	46.4	5.6	55.5	3.4	4.6	4.2
30-34	44.8	5.6	57.0	3.7	5.1	7.4
35-39	38.0	5.5	71.0	1.1	2.7	5.2
40-44	38.5	4.7	73.9	4.7	8.6	4.7
45-49	33.7	4.9	70.7	2.2	6.0	4.9
≥ 50	31.6	4.9	57.8	2.4	4.9	4.9
Total	41.5	4.1	35.0	2.1	3.9	3.5
<18	37.7	2.6	10.4	0.9	2.5	1.3
≥ 18	44.6	5.3	54.6	3.1	5.1	5.3

Table 16: Frequency in % of patients with microbiological examination 2017

Lung infections

7c. Atypical mycobacteria (without lung transplant)

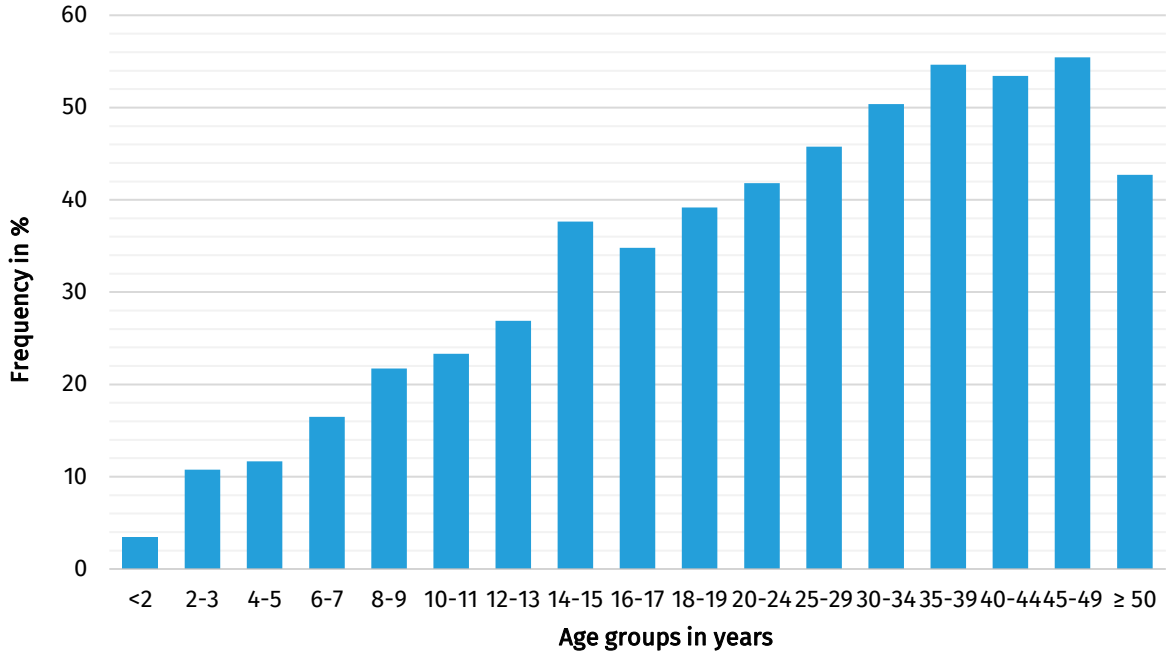

Figure 18: Age-related frequency in % of examinations for atypical mycobacteria 2017

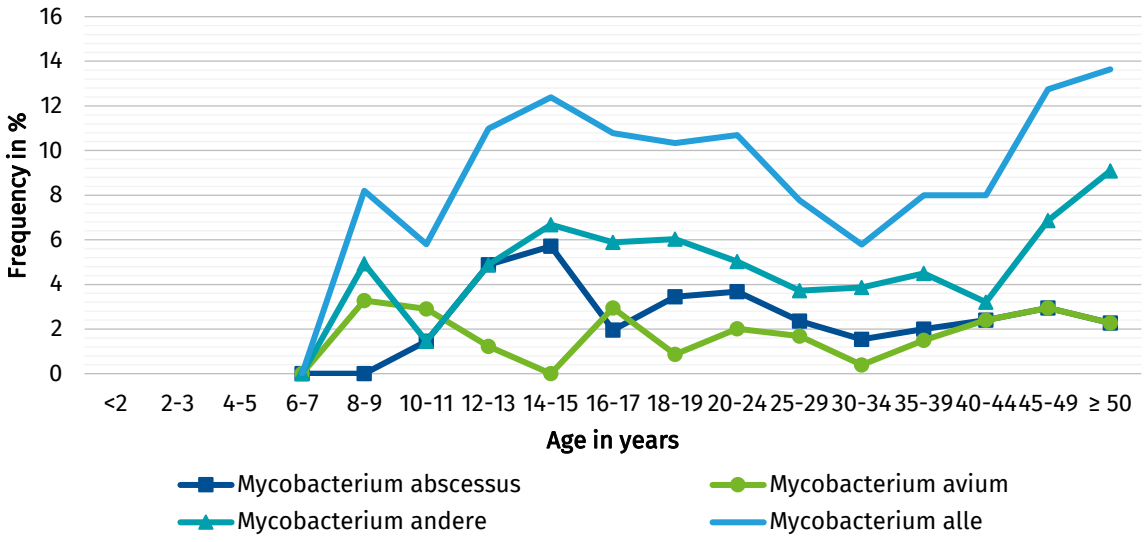

Figure 19: Age-related frequency in % of patients with examinations for atypical mycobacteria 2017

07

Lung infections

7c. Atypical mycobacteria (without lung transplant)

Age in years	Examination on atypical mycobacteria	Detection of		
		Mycobacterium abscessus[1]	Mycobacterium avium[1]	Mycobacterium andere[1]
<2	3.5	0.0	0.0	0.0
2-3	10.8	0.0	0.0	0.0
4-5	11.7	0.0	0.0	0.0
6-7	16.5	0.0	0.0	0.0
8-9	21.7	0.0	3.3	4.9
10-11	23.3	1.5	2.9	1.5
12-13	26.9	4.9	1.2	4.9
14-15	37.6	5.7	0.0	6.7
16-17	34.8	2.0	2.9	5.9
18-19	39.2	3.5	0.9	6.0
20-24	41.8	3.7	2.0	5.0
25-29	45.8	2.4	1.7	3.7
30-34	50.4	1.5	0.4	3.9
35-39	54.6	2.0	1.5	4.5
40-44	53.4	2.4	2.4	3.2
45-49	55.4	2.9	2.9	6.9
≥ 50	42.7	2.3	2.3	9.1
Total	35.7	2.5	1.6	4.6
<18	21.4	2.4	1.5	3.9
≥ 18	47.0	2.6	1.6	4.8

Table 17: Frequency in % of patients with examinations for atypical mycobacteria 2017

[1]Frequency in % of patients related to atypical mycobacterial examination

Complications extended

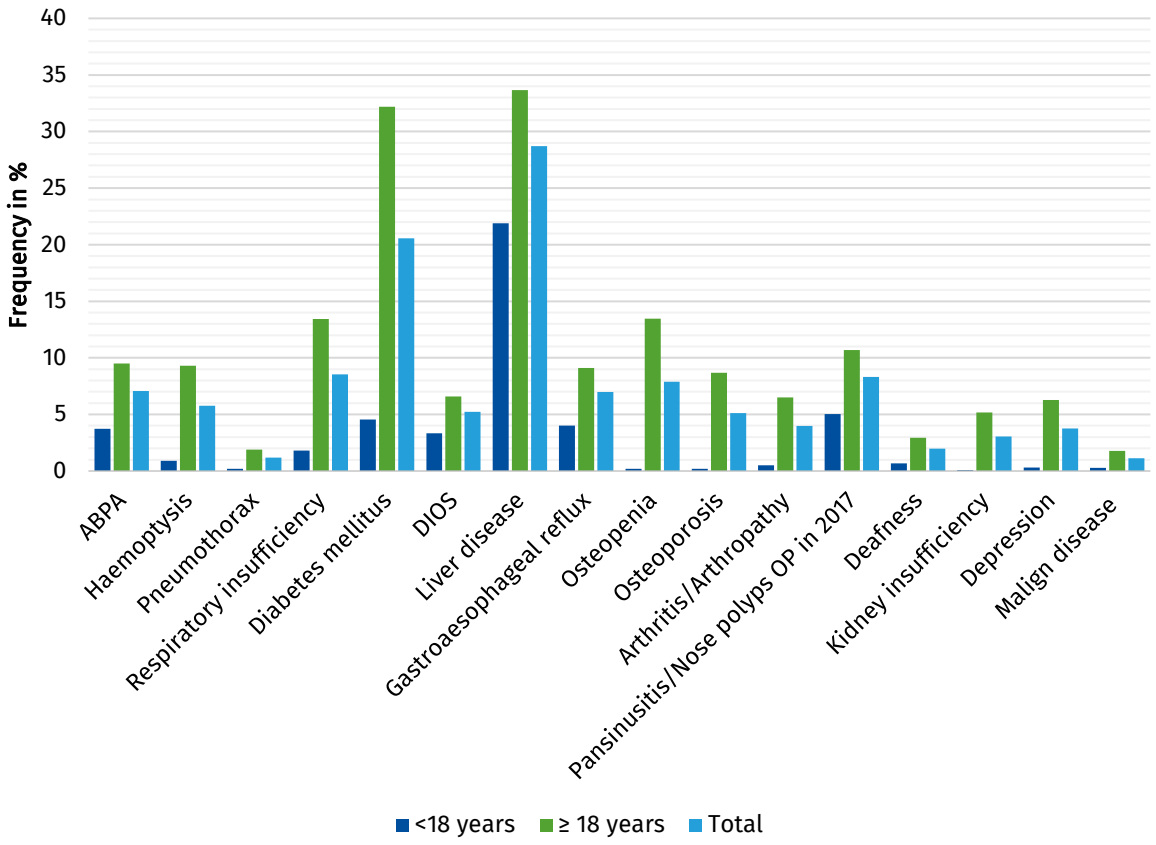

Figure 20: Frequency of various complications in % of patients by age groups <18 and ≥18 years without pancreatic insufficiency 2017

08

Complications extended

Complication	<18 years	≥ 18 years	Total
ABPA	3.7	9.5	7.1
Haemoptysis	0.9	9.3	5.8
of these, severe cases	8.7	4.9	5.2
Pneumothorax	0.2	1.9	1.2
of these, requiring drainage	60.0	47.0	47.9
Respiratory insufficiency	1.8	13.4	8.6
of these, partial insufficiency	60.9	68.1	67.5
of these, global insufficiency	13.0	21.4	20.7
Exocrine pancreatic insufficiency	86.2	87.4	86.9
Diabetes mellitus	4.6	32.2	20.6
of these, Typ III	89.7	94.1	93.7
of these, not Typ III	10.3	5.9	6.3
DIOS	3.3	6.6	5.2
Liver disease	21.9	33.7	28.7
of these, liver cirrhosis	14.6	20.2	18.4
of these, with portal hypertension	5.9	8.5	7.7
of these, without portal hypertension	4.5	5.1	4.9
Gastroaesophageal reflux	4.0	9.1	7.0
Bone disease			
Osteopena	0.2	13.5	7.9
Osteoporosis	0.2	8.7	5.1
Arthritis/Arthropathty	0.5	6.5	4.0
Pansinusitis / Nose polyps OP in 2017	5.0	10.7	8.3
Deafness	0.7	2.9	2.0
Kidney insufficiency	0.1	5.2	3.0
Depression	0.3	6.3	3.8
Malign disease	0.3	1.8	1.1

Table 18: Frequencies in % of patients 2017

Therapies

9a. Basic therapy

9a.i. Children and adolescents

Basic therapy	0-5 years	6-11 years	12-17 years	Total
DNAse	15.9	54.5	67.8	47.8
Mannitol	0.1	0.6	1.7	0.8
Hypertonic saline solution	89.9	94.0	87.2	90.4
of these 3-5.7%	48.6	33.2	28.5	36.1
of these >=5.8%	51.4	66.7	71.4	63.8
ß2-sympathomimetics				
Short-term effect (SABA)	67.1	72.5	71.1	70.4
Long-term effect (LABA)	6.9	20.8	32.7	20.9
Anticholinergic drugs	11.3	16.1	16.1	14.7
Anti-Staphylococci therapy	7.5	10.1	11.6	9.9
Steroids				
Nasal	8.3	20.3	21.4	17.1
Oral	0.4	2.2	5.1	2.7
Inhalative	11.6	23.8	29.2	22.1
Vitamins				
Vitamin A	79.0	79.0	80.6	79.5
Vitamin D	95.5	94.2	95.3	95.0
Vitamin E	75.5	75.2	79.0	76.6
Vitamin K	67.6	62.5	68.1	66.0

Table 19: Frequency in % of patients with basic therapy <18 years 2017

09

Therapies

9a. Basic therapy

9a.ii. Adults

Basic therapy	18-29 years	30-39 years	≥ 40 years	Total
DNAse	60.6	49.2	43.7	53.8
Mannitol	9.3	8.1	6.4	8.4
Hypertonic saline solution	76.4	67.2	59.1	70.2
of these 3-5.7%	24.4	26.4	25.9	25.2
of these ≥5.8%	73.8	72.0	71.1	72.8
ß2-sympathomimetics				
Short-term effect (SABA)	65.5	65.4	65.4	65.4
Long-term effect (LABA)	51.4	59.1	65.0	56.4
Anticholinergic drugs	35.0	48.1	57.1	43.3
Anti-Staphylococci therapy	10.5	9.9	10.1	10.2
Steroids				
Nasal	20.0	18.6	17.0	19.0
Oral	11.4	19.5	23.4	16.2
Inhalativ	40.8	51.7	56.8	47.3
Vitamins				
Vitamin A	71.2	61.5	51.4	64.3
Vitamin D	91.9	91.2	86.2	90.5
Vitamin E	69.4	59.8	50.7	62.8
Vitamin K	58.5	51.5	43.5	53.4

Table 20: Frequencies in % of patients with basic therapy >18 years 2017

Therapies

9b. Indication therapy

9b.i. Children and adolescents

Indication therapy	0-5 years	6-11 years	12-17 years	Total
Ivacaftor* *in case of gating mutation*	76.9 (2-5 years)	74.3	79.2	76.4
Lumacaftor/Ivacaftor *in case of F508del/F508del*	0.0	2.3	22.8	9.3
Inhalative antibiotics *in case of chronic Pseudomonas infection*	81.0	93.5	90.7	90.8
Azithromycin *in case of chronic Pseudomonas infection*	9.5	10.4	24.7	19.2
Ursodesoxycholic acid *in case of liver disease*	84.3	90.2	87.8	88.2
Dietary measures *in case of Diabetes mellitus*	0.0	38.5	28.2	29.3
Insulin therapy *in case of Diabetes mellitus*	0.0	69.2	66.0	66.4
Orale antidiabetics *in case of Diabetes mellitus*	0.0	7.7	11.7	11.2
Pancreatic enzymes *in case of exocrine pancreatic insufficiency*	99.0	99.1	98.6	98.9
Additional nutration	50.8	57.2	60.0	56.6
in case of being underweight				
Oral supplementary food	49.2	53.1	54.2	52.5
PEG	1.5	6.2	13.2	7.7
Proton pump inhibitors *in case of gastroesophageal reflux*	77.8	86.7	85.4	85.3
Polyenthylene glycol *in case of DIOS*	64.7	60.0	44.7	54.1
Calcium *in case of osteopenia/osteoporosis*	100.0	0.0	33.3	40.0
Oxygen therapy *in case of respiratory insufficiency*	0.0	30.8	46.4	37.0

Table 21: Frequency in % of patients with indication therapies < 18 years 2017

* Ivacaftor is approved in Germany from the age of 2 for gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. and from the 18th year of age, for R117H.

09

Therapies

9b. Indication therapy

9b.ii. Adults

Indication therapy	18-29 years	30-39 years	≥ 40 years	Total
Ivacaftor* *in case of gating mutation*	69.7	68.8	56.8	66.3
Lumacaftor/Ivacaftor *in case of F508del/F508del*	29.4	29.6	23.3	28.3
Inhalative antibiotics *in case of chronic Pseudomonas infection*	88.7	88.0	87.4	88.2
Azithromycin *in case of chronic Pseudomonas infection*	34.7	43.2	41.6	39.2
Ursodesoxycholic acid *in case of liver disease*	82.9	78.7	76.8	80.6
Dietary measures *in case of Diabetes mellitus*	20.0	21.2	21.9	21.0
Insulin therapy *in case of Diabetes mellitus*	71.3	78.0	83.4	77.2
Orale antidiabetics *in case of Diabetes mellitus*	7.7	9.3	7.4	8.1
Pancreatic enzymes *in case of exocrine pancreatic insufficiency*	97.2	96.6	96.1	96.8
Additional nutration	56.3	54.5	48.0	54.8
in case of being underweight				
Oral supplementary food	48.7	50.3	41.3	48.2
PEG	11.0	5.4	5.3	8.7
Proton pump inhibitors *in case of gastroesophageal reflux*	81.2	79.6	84.0	81.6
Polyenthylene glycol *in case of DIOS*	32.7	39.7	36.2	35.5
Calcium *in case of osteopenia/osteoporosis*	40.3	53.1	54.4	50.0
Bisphosphonate *in case of osteoporosis*	12.0	21.8	40.0	26.6
Oxygen therapy *in case of respiratory insufficiency*	65.0	65.8	69.3	66.5
Non-invasive ventilation *In case of respiratory global insufficiency*	40.5	36.8	60.0	44.0

Table 22: Frequency in % of patients with indication therapies ≥ 18 years 2017
* Ivacaftor is approved in Germany from the age of 2 for gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. and from the 18th year of age, for R117H.

Mortality

Lifetime is described by median age at death, median survival and average age-specific life expectancy. On the basis of internationally accepted and comparable analytical methods, we would like to present these parameters in the present collective report. Due to a striking difference in deaths between 2016 (63) and 2017 (48), as well as the higher number of patients lost to follow-up, we chose to report the current median age of death for year 2017, and the median survival age and life expectancy for the period 2012–2016.

10a. Age of death 2017

The median age of death for a given year is that age at which one-half of the patients have died. In the reporting years 2017 and 2016, the median age at death was 32 and 33, respectively.

In 2017, 48 patients (25 girls/women and 23 boys/men) died. The main causes of death were cardiopulmonary (75.0%) and malignant diseases (4.2%). In 8.3% of the cases there were other or unknown causes. 4,2% died as a result of accidents. The age at death is distributed as follows:

	Number	Mean value	Median	Minimum	Maximum	Perzentil 25	Perzentil 75
Age at time of death in full years	48	31.77	32	4	54	23	39

Table 23: Age of death 2017

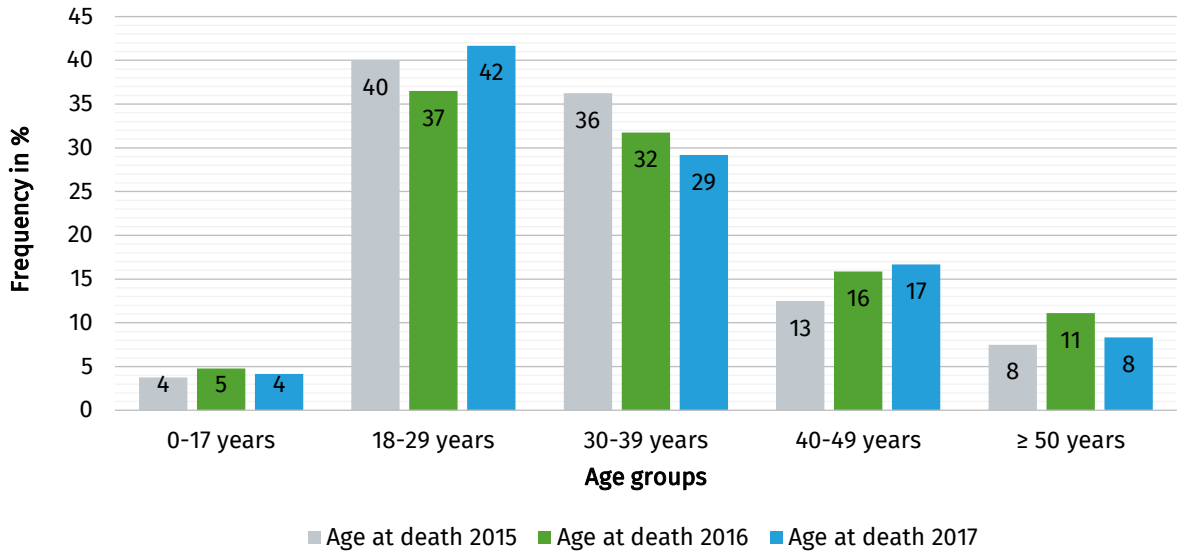

Figure 21: Frequency in % of deceased patients by age groups in 2017

10

Mortality

Alter	Number	Percent
0-17 years	<5	4.2
18-29 years	20	41.7
30-39 years	14	29.2
40-49 years	8	16.7
≥ 50 years	4	8.3
Total	48	100.0

Table 24: Frequency of deceased patients by age groups 2017

10b. Median survival age

The median survival age is the estimated age beyond which merely 50% of the patients will still be alive. To compensate for variations in the number of deaths per year, a COX PH regression analysis according to Sykes (Journal of Clinical Epidemiology 2016; 70: 206) is performed over a 5-year period. In the 5-year window between 2012 and 2016, 7181 people with cystic fibrosis (including transplanted patients) and 423 deaths were recorded. 71 patients (1%) were lost to follow-up. The median survival age amounted to 47.5 years (confidence interval: 44.8 to 49.7).

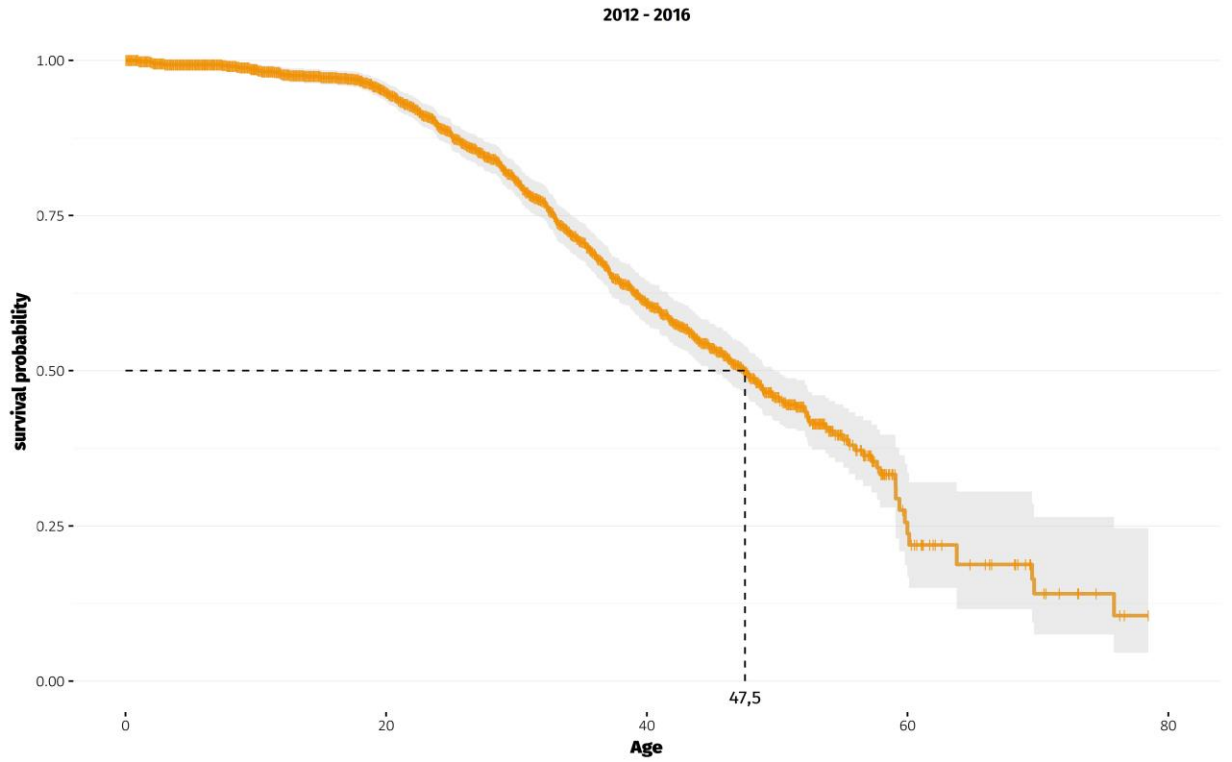

Figure 22: Median survival age for CF patients 2012-2016

Mortality

10c. Life expectancy

Life expectancy is a statistical measure of the average time a person is still expected to live (i.e. remaining time from a certain age to death). It is calculated for a given period based on current and age-specific death rates. Currently, the life expectancy of a healthy male neonate in Germany is 78 years, and that of a female neonate 83 years (www.statista.de). Life expectancy varies depending on age and does not equal the median survival age.

All parameters refer to the very heterogeneous population of cystic fibrosis patients in Germany. Hence, they allow only limited conclusions regarding the individual patients. According to the literature, the key influencing factors include the patient's age, the gene mutation present and the exocrine pancreatic function. All calculations are based on the current death rate, which has fortunately been steadily decreasing over the past years.

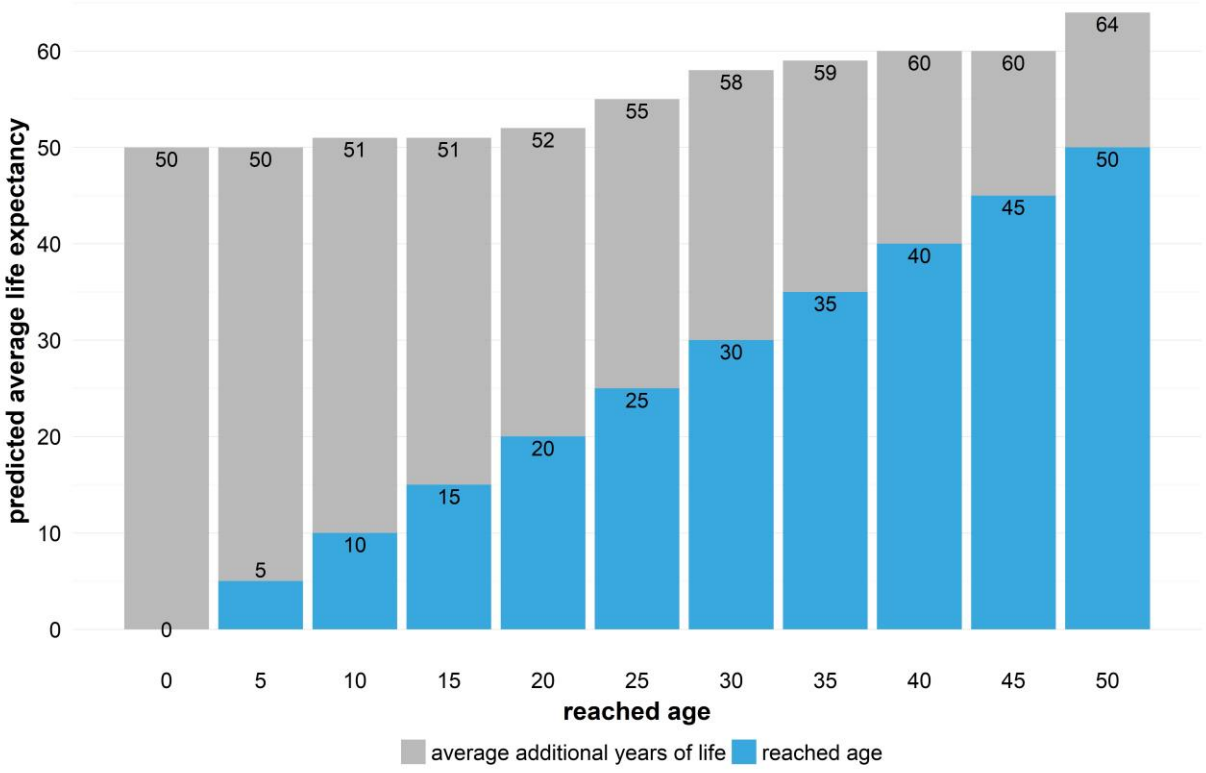

Figure 23: Predicted average life expectancy of CF patients 2012-2016

11

Structure of care

In the reporting year 2017, 91 institutions participated in the cystic fibrosis register. 47 CF-sites cared for less than 50 patients and 44 CF-sites cared for more than 50 patients. Over 80% of the patients documented in the register are cared for in the 44 CF-sites.

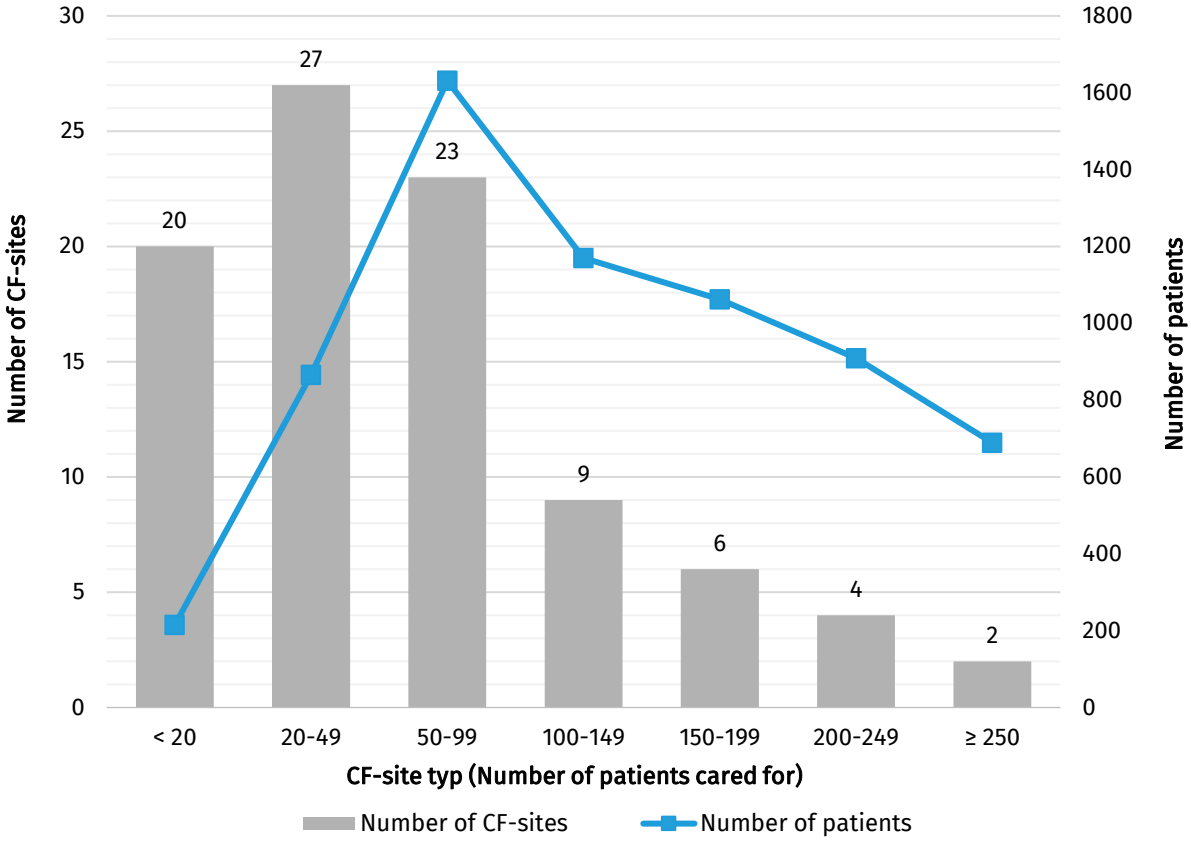

Figure 24: Number of documented patients and number of facilities 2017

Structure of care

	Yes	No	unknown
Physiotherapy *in the outpatient department*	58.0	39.0	3.0
Nutration therapy *in the outpatient department*	37.3	61.4	1.3
Psychosocial support *in the outpatient department*	41.5	55.6	2.9
Imaging			
Thorax	54.9	44.9	0.2
Abdomen	55.5	44.3	0.2
Laboratory	94.1	5.8	0.1
Rehabilitation stay	8.7	85.0	6.3
Anxiety and depression screening	12.5	86.1	1.4

Table 25: Outpatient care in % in the reporting year 2017

	0	1	2	3	4	5+	unknown
CF-relevant hospital stays	65.1	18.0	7.4	3.3	1.7	1.4	3.0
Antibiotically treated exacerbations	40.7	21.4	15.5	8.3	4.8	5.4	3.9

Table 26: Frequency in % of CF patients with the mentioned number of events 2017

12

Glossary

ABPA (Allergic bronchopulmonary aspergillosis)	When a person develops an allergic reaction to Aspergillus fumigatus.
Anticholinergic drugs	An anticholinergic medicine has a relaxant effect on the smooth musculature and inhibits secretion.
Arthritis	A condition which causes pain and inflammations in the joints.
Arthropathy	A condition which causes pain in the joints.
Pancreas	An organ in the digestive system which produces insulin and digestive enzymes.
Beta sympathomimetics	Beta sympathomimetics are drugs Drug substanceswhich stimulate the Beta receptors of the Sympathetic nervous system.
BMI (Body Mass Index)	A measured value for the assessment of the body weight of a person in relation to its body size
Burkholderia cepacia	Burkholderia cepacia is one of a species of bacteria in the Burkholderia genus. Several of these bacteria are a potential threat to the health of people with cystic fibrosis.
CF - Cystic fibrosis	Cystic fibrosis
CFTR (Regulator of the transmembrane conductivity in case of cystic fibrosis)	A protein on the cell surface which controls the saline and water levels in a cell. The gene which causes cystic fibrosis is the blueprint for the CFTR protein. Every person has two copies of the gene for CFTR. In order for someone to be born with cystic fibrosis, both CFTR genes must be affected by a mutation causing CF.
Enzymes	Biological molecules present in the body which support complex reactions such as the digestion of foods.
FEV1 (one-second capacity)	The FEV1 (Forced Expiratory Pressure in 1 Second) is the largest-possible quantity of air which you can force out of your lungs within 1 second. The FEV1 value is a part of the lung function, and can be measured within the scope of a lung function test.
FEV1% predicted	The FEV1% is the percent value of the average FEV1 which healthy people of the same age, gender and length can achieve. Normally, this lies between 80-120%.
Gastroesophageal reflux disease	A chronic symptom of damage through stomach acid which rises up from the gastric mucosa.
Genotype	A characteristic part of the genetic structure of a cell, an organism or an individual.

Glossary

GLI equations	The equation of the Global Lung Initiative takes into consideration the following factors for calculation of the FEV1%: absolute FEV1, age, gender, size and ethnicity.
Haemophilus influenzae	Haemophilus influenza is a bacterium which can cause severe illness.
Haemoptysis	Coughing up blood.
Mutation	A mutation is an alteration to a gene. If both parents of a child bear a mutation which causes CF, there is a 25% chance that the child will have cystic fibrosis. There are over 1,400 different mutations of the CFTR gene.
Nose polyps	Small, sack-shaped growths caused through chronic inflammations of the nasal mucosa.
New-born screening	The new-born screening is an examination of new-born babies in order to detect congenital diseases such as cystic fibrosis at an early stage.
Non-tuberculous mycobacteria (NTM)	A mycobacteria which does not trigger tuberculosis but can still be the cause of respiratory infections. Several types are known.
Osteopenia	A less severe disease than osteoporosis, through which the mineral content of bones is reduced.
Osteoporosis	A condition in which the bones become brittle due to the loss of tissue.
Percentile	A percentile indicates where a value is relative to the rest of the data. If a value lies higher than 90% of the remaining data, we speak of the 90th percentile.
Pneumothorax	A collection of air in the cavity between the lung and the chest wall which can lead to a collapsed lung on the affected side.
Prevalence	The total number of people with this disease over the past 12 months.
Pseudomonas aeruginosa	A tenacious bacterial strain which seldom affects healthy people, but which can lead to a multitude of infections in case of a weakened immune system.
Liver cirrhosis	A chronic liver disease.