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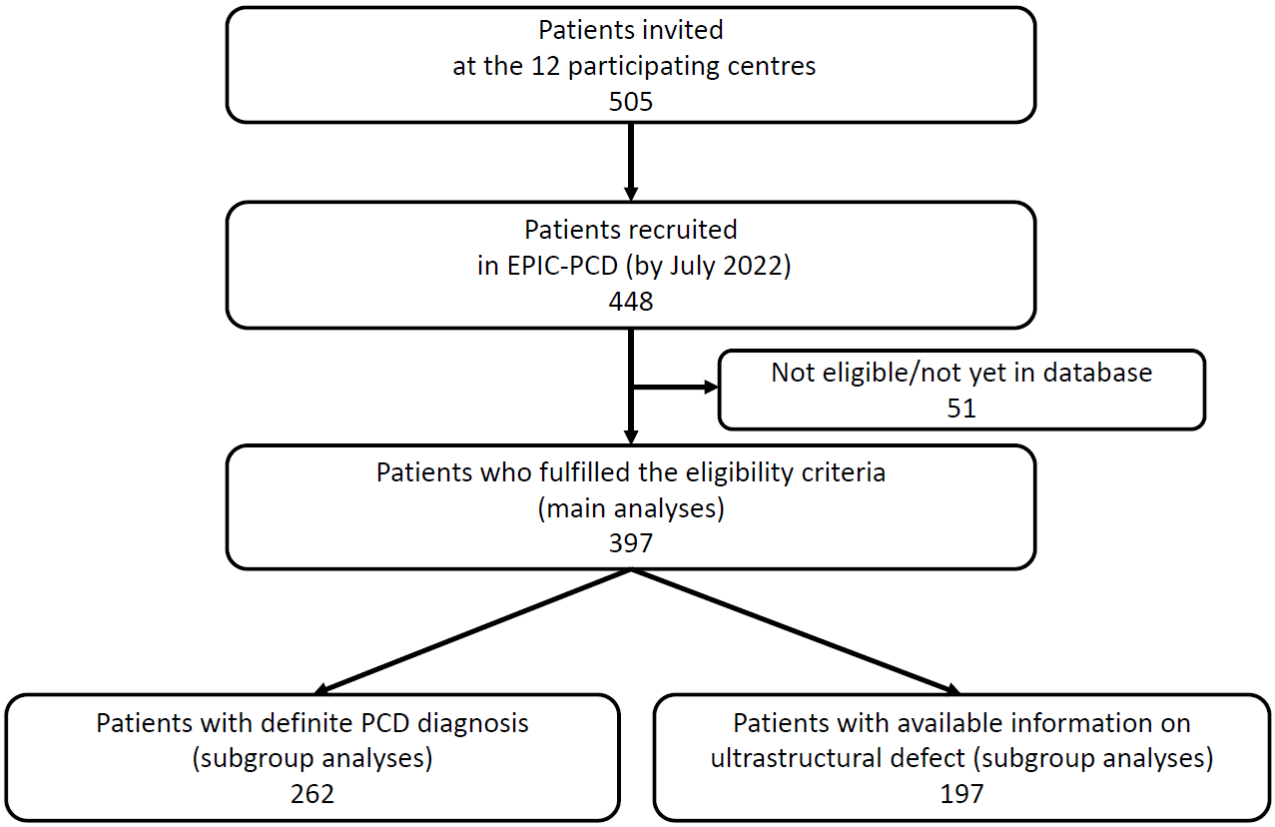


eFigure 1 Flowchart of patients with PCD who were invited and participated in EPIC-PCD and the study

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia

eTable 1 Centre and diagnostic information of EPIC-PCD participants, overall and by age group (N=397)

	Total N (%)	Age 0-6 y N (%)	Age 7-14 y N (%)	Age 15-30 y N (%)	Age 31-50y N (%)	Age >50 y N (%)
Number of participants	**397 (100)**	**44 (100)**	**130 (100)**	**157 (100)**	**43 (100)**	**23 (100)**
Centre						
Amsterdam	26 (7)	3 (7)	12 (9)	11 (7)	0 (0)	0 (0)
Ankara	60 (15)	5 (11)	23 (18)	32 (20)	0 (0)	0 (0)
Berlin	43 (11)	8 (18)	4 (3)	16 (10)	10 (23)	5 (22)
Bern	7 (2)	1 (2)	2 (2)	4(3)	0 (0)	0 (0)
Cyprus	22 (6)	3 (7)	3 (2)	6 (4)	6 (14)	4 (17)
Istanbul	66 (17)	4 (9)	26 (20)	34 (22)	2 (5)	0 (0)
Leuven	12 (3)	0 (0)	5 (4)	6 (4)	1 (2)	0 (0)
Liege	10 (2)	1 (2)	4 (3)	3 (2)	2 (5)	0 (0)
Oslo	39 (9)	3 (7)	22 (17)	14 (9)	0 (0)	0 (0)
Paris	53 (13)	0 (0)	7 (5)	17 (11)	20 (47)	9 (39)
Southampton	43 (11)	14 (32)	22 (17)	7 (4)	0 (0)	0 (0)
Valencia	16 (4)	2 (5)	0 (0)	7 (4)	2 (5)	5 (22)
Nasal nitric oxide measurement						
Indicative for PCD	249 (63)	22 (50)	76 (59)	103 (65)	32 (74)	16 (70)
Not indicative for PCD	16 (4)	1 (2)	3 (2)	9 (6)	3 (7)	0 (0)
Not performed/pending	132 (33)	21 (48)	51 (39)	45 (29)	8 (19)	7 (30)
Transmission Electron Microscopy						
Hallmark defect	135 (34)	13 (30)	42 (32)	53 (34)	17 (40)	10 (43)
Other defect	21 (5)	0 (0)	9 (7)	7 (4)	3 (7)	2 (9)
Normal ultrastructure	41 (10)	9 (20)	15 (12)	9 (6)	5 (11)	3 (13)
Not performed/pending	200 (51)	22 (50)	64 (49)	88 (56)	18 (42)	8 (35)
High-speed videomicroscopy analysis						
Indicative for PCD	207 (52)	30 (68)	62 (48)	79 (51)	19 (44)	17 (74)
Other/unclear	13 (3)	4 (9)	6 (5)	2 (1)	1 (2)	0 (0)
Normal motility	6 (2)	1 (2)	2 (2)	2 (1)	1 (2)	0 (0)
Not performed/pending	170 (43)	9 (21)	59 (45)	74 (47)	22 (52)	6 (26)
Genetic testing						
No pathogenic variants	32 (8)	5 (11)	12 (9)	11 (7)	2 (5)	2 (9)
Results pending	13 (3)	1 (2)	5 (4)	7 (4)	0 (0)	0 (0)
Biallellic pathogenic variants/ compound heterozygosity	192 (48)	21 (48)	61 (47)	70 (45)	28 (65)	12 (52)
Heterozygous variant	43 (11)	3 (7)	7 (5)	25 (16)	4 (9)	4 (17)
Not performed	117 (30)	14 (32)	45 (35)	44 (28)	9 (21)	5 (22)
Immunofluorescence						
Indicative for PCD	36 (9)	7 (16)	6 (5)	21 (13)	2 (5)	0 (0)
Not indicative for PCD	36 (9)	8 (18)	17 (13)	9 (6)	1 (2)	1 (4)
Not performed/pending	325 (82)	29 (66)	107 (82)	127 (81)	40 (93)	22 (96)

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia. y: years. Characteristics are presented as N and column %.

eTable 2: Genetic mutations reported in EPIC-PCD participants with biallelic pathogenic variants or compound heterozygosity (N=192)

Genetic mutation	N (%)
DNAH5	36 (19)
DNAH11	24 (12)
CCDC40	23 (12)
HYDIN	13 (7)
CCDC39	10 (5)
RSPH4A	9 (5)
DNAI1	9 (5)
CCNO	8 (4)
RSPH9	8 (4)
DNAAF1	6 (3)
RSPH3	5 (3)
CCDC114	5 (3)
DNAH9	4 (2)
C11ORF70	4 (2)
TTC25	3 (2)
DNAI2	5 (3)
DNAAF11	3 (2)
CCDC65	2 (1)
DNAFF2	2 (1)
CCDC103	1 (0.5)
ZMYND10	1 (0.5)
DRC1	1 (0.5)
DNAH1	1 (0.5)
DNAAF3	1 (0.5)
DNAAF5	1 (0.5)
ARMC4	1 (0.5)
CCDCC151	1 (0.5)
DCLRE1C	1 (0.5)
FOXJ1	1 (0.5)
Total	**192 (100)**

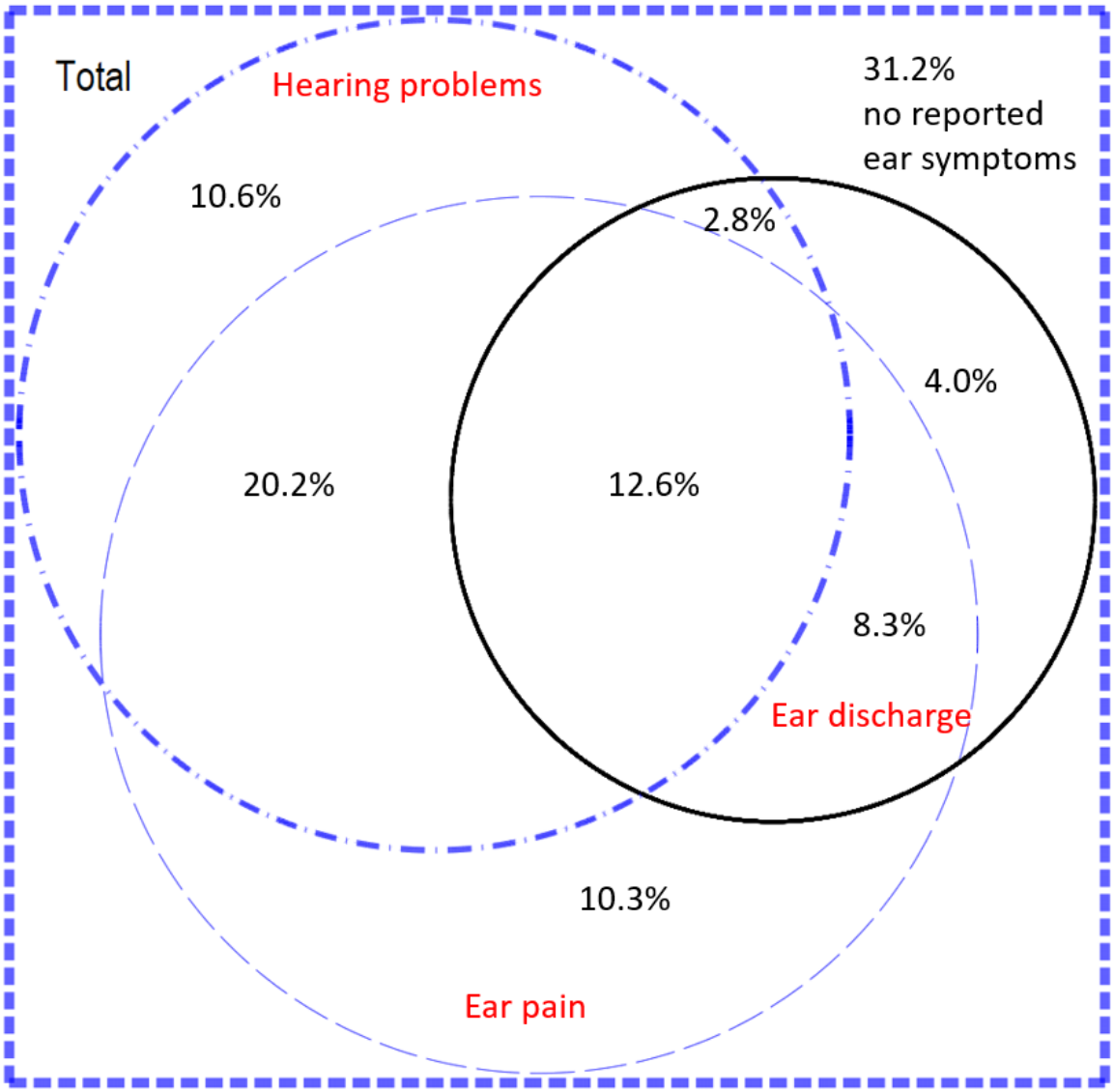
EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia.

eTable 3: Frequency of self- and parent-reported ear symptoms of EPIC-PCD participants, overall and by age group (N=397)

	Total N (%)	Age 0-6 y N (%)	Age 7-14 y N (%)	Age 15-30 y N (%)	Age 31-50 y N (%)	Age >50 y N (%)	Cramér's V (95%CI)[a]
Number of participants	397 (100)	44 (100)	130 (100)	157 (100)	43 (100)	23 (100)	
Ear pain							
Daily	14 (3)	0 (0)	2 (1)	6 (4)	4 (9)	2 (9)	0.17 (0.11-0.19)
Often	36 (9)	2 (4)	10 (8)	16 (10)	3 (7)	5 (22)	
Sometimes	70 (18)	6 (14)	25 (19)	21 (13)	9 (21)	9 (39)	
Rarely	84 (21)	6 (14)	22 (17)	37 (24)	16 (37)	3 (13)	
Never/not reported	193 (49)	30 (68)	71 (55)	77 (49)	11 (26)	4 (17)	
Ear discharge							
Daily	7 (2)	1 (2)	3 (2)	1 (1)	1 (2)	1 (4)	0.12 (0.08-0.13)
Often	15 (4)	0 (0)	2 (2)	7 (4)	3 (7)	3 (13)	
Sometimes	40 (10)	2 (5)	21 (16)	13 (8)	3 (7)	1 (4)	
Rarely	48 (12)	4 (9)	12 (9)	22 (14)	6 (14)	4 (17)	
Never/not reported	287 (72)	37 (84)	92 (71)	114 (73)	30 (70)	14 (61)	
Hearing problems							
Daily	37 (9)	2 (5)	10 (8)	9 (6)	7 (16)	9 (39)	0.21 (0.13-0.24)
Often	38 (10)	4 (9)	10 (8)	10 (6)	8 (18)	6 (26)	
Sometimes	61 (15)	5 (11)	25 (19)	17 (11)	9 (21)	5 (22)	
Rarely	47 (12)	1 (2)	14 (10)	26 (16)	5 (12)	1 (4)	
Never/not reported	214 (54)	32 (73)	71 (55)	95 (61)	14 (33)	2 (9)	

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia. y: years. Symptoms are presented as N and column %.

a: Cramér's V and bias-corrected 95% confidence intervals based on chi-squared test of independence; it ranges from 0 (no association) to 1 (strong association).



eFigure 2 Venn diagram showing overlap of self- and parent-reported symptoms of EPIC-PCD participants (N=397)

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia

eTable 4: Frequency of self- and parent-reported ear symptoms of EPIC-PCD participants with definite PCD diagnosis, overall and by age group (N=262)

	Total N (%)	Age 0-6 y N (%)	Age 7-14 y N (%)	Age 15-30 y N (%)	Age 31-50 y N (%)	Age >50 y N (%)	Cramér's V (95%CI)[a]
Number of participants	262 (100)	29 (100)	81 (100)	102 (100)	35 (100)	15 (100)	
Ear pain							
Daily	10 (4)	0 (0)	1 (1)	4 (4)	4 (11)	1 (7)	0.19 (0.12-0.21)
Often	18 (7)	0 (0)	5 (6)	8 (8)	2 (6)	3 (20)	
Sometimes	45 (17)	4 (14)	15 (19)	11 (11)	9 (26)	6 (40)	
Rarely	57 (22)	4 (14)	14 (17)	27 (26)	10 (28.5)	2 (13)	
Never/not reported	132 (50)	21 (72)	46 (57)	52 (51)	10 (28.5)	3 (20)	
Ear discharge							
Daily	5 (2)	0 (0)	2 (2)	1 (1)	1 (3)	1 (7)	0.14 (0.09-0.15)
Often	8 (3)	0 (0)	1 (1)	3 (3)	2 (6)	2 (13)	
Sometimes	26 (10)	2 (7)	13 (16)	8 (8)	3 (9)	0 (0)	
Rarely	33 (13)	2 (7)	7 (9)	16 (16)	5 (14)	3 (20)	
Never/not reported	190 (72)	25 (86)	58 (72)	74 (72)	24 (68)	9 (60)	
Hearing problems							
Daily	27 (10)	2 (7)	7 (9)	7 (7)	7 (20)	4 (27)	0.22 (0.14-0.25)
Often	25 (10)	2 (7)	6 (8)	5 (5)	7 (20)	5 (33)	
Sometimes	44 (17)	3 (10)	18 (22)	11 (11)	9 (26)	3 (20)	
Rarely	31 (12)	0 (0)	10 (12)	17 (16)	3 (8)	1 (7)	
Never/not reported	135 (51)	22 (76)	40 (49)	62 (61)	9 (26)	2 (13)	

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia. y: years. Symptoms are presented as N and column %.

a: Cramér's V and bias-corrected 95% confidence intervals based on chi-squared test of independence; it ranges from 0 (no association) to 1 (strong association).

eTable 5: Otoscopy findings of EPIC-PCD participants with definite diagnosis, overall and by age group (N=255)

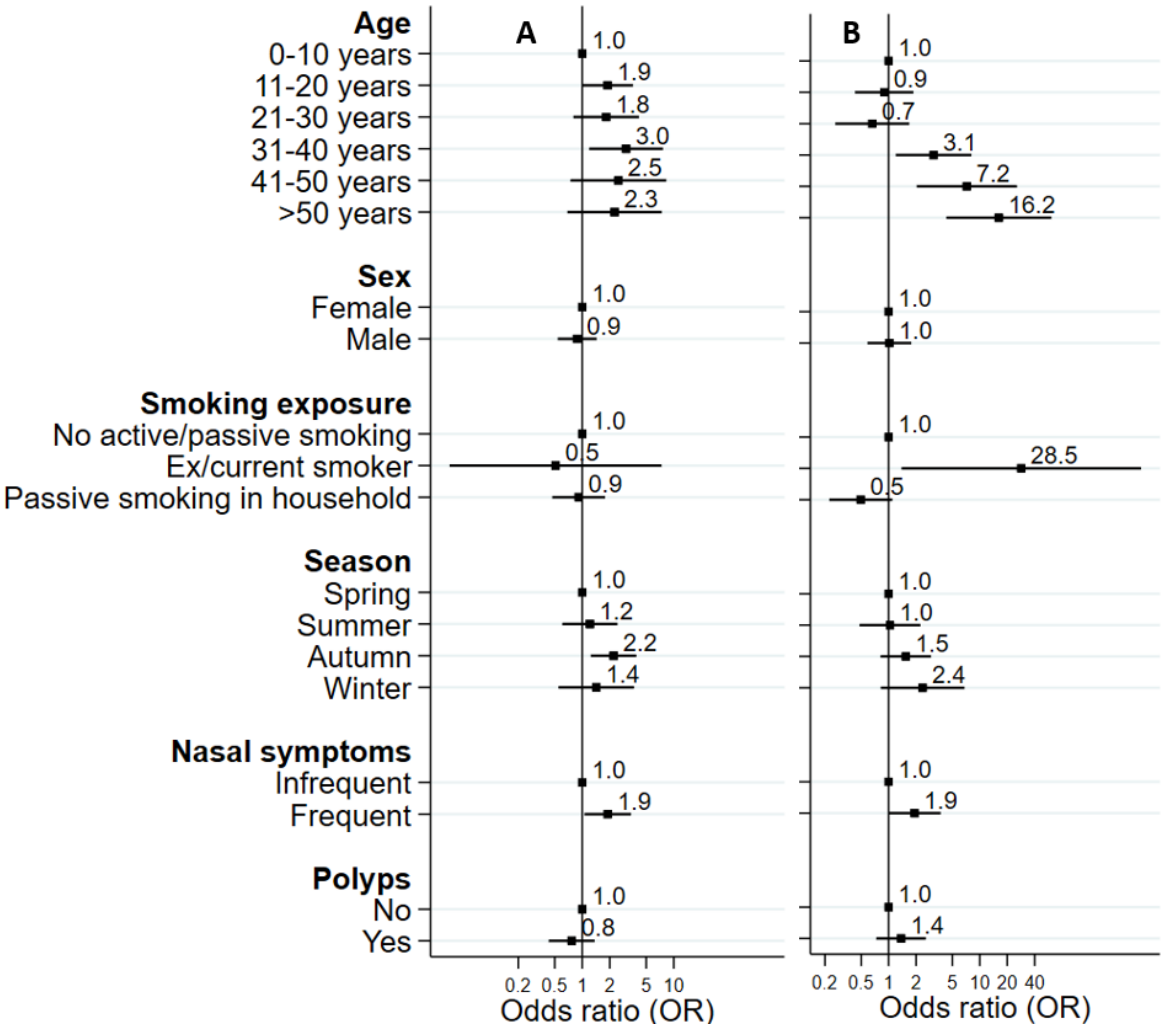
	Total N (%)	Age 0-6 y N (%)	Age 7-14 y N (%)	Age 15-30 y N (%)	Age 31-50 y N (%)	Age >50 y N (%)	Cramér's V (95%CI)[a]
Number of participants	255 (100)	28 (100)	78 (100)	102 (100)	34 (100)	13 (100)	
Acute otitis media							
Bilateral	1 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	
Unilateral	1 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0.09 (0.02-0.10)
No	243 (96)	26 (93)	75 (96)	96 (94)	33 (97)	13 (100)	
Not assessed	10 (4)	2 (7)	2 (3)	5 (5)	1 (3)	0 (0)	
Ear discharge							
Bilateral	10 (4)	1 (4)	4 (5)	4 (4)	0 (0)	1 (8)	
Unilateral	15 (6)	0 (0)	7 (9)	6 (6)	1 (3)	1 (8)	0.10 (0.08-0.10)
No	228 (89)	27 (96)	67 (86)	91 (89)	32 (94)	11 (84)	
Not assessed	2 (1)	0 (0)	0 (0)	1 (1)	1 (3)	0 (0)	
Tympanic perforation							
Bilateral	5 (2)	0 (0)	2 (3)	2 (2)	0 (0)	1 (8)	
Unilateral	12 (5)	0 (0)	7 (9)	6 (6)	2 (6)	0 (0)	0.13 (0.08-0.16)
No	228 (90)	25 (89)	68 (87)	91 (89)	32 (94)	12 (92)	
Not assessed	7 (3)	3 (11)	1 (1)	3 (3)	0 (0)	0 (0)	
Retracted membrane							
Bilateral	18 (7)	0 (0)	5 (6.5)	9 (9)	1 (3)	3 (23)	
Unilateral	14 (6)	1 (3)	5 (6.5)	5 (5)	1 (3)	2 (15)	0.19 (0.11-0.23)
No	212 (83)	22 (79)	67 (86)	84 (82)	32 (94)	7 (54)	
Not assessed	11 (4)	5 (18)	1 (1)	4 (4)	0 (0)	1 (8)	
Otitis media with effusion							
Bilateral	61 (23)	9 (32.5)	25 (31)	19 (17)	4 (12)	4 (31)	
Unilateral	20 (8)	1 (5)	9 (10)	10 (10)	0 (0)	0 (0)	0.15 (0.09-0.16)
No	160 (64)	15 (55)	39 (52)	69 (70)	29 (85)	8 (61)	
Not assessed	14 (5)	3 (7.5)	5 (7)	4 (3)	1 (3)	1 (8)	
Tympanic sclerosis							
Bilateral	35 (14)	0 (0)	7 (9)	12 (12)	12 (35)	4 (31)	
Unilateral	12 (5)	0 (0)	5 (6)	6 (6)	1 (3)	0 (0)	0.18 (0.12-0.22)
No	186 (73)	22 (79)	60 (77)	75 (74)	20 (59)	9 (69)	
Not assessed	22 (8)	6 (21)	6 (8)	9 (98)	1 (3)	0 (0)	
Tympanostomy tubes							
Bilateral	8 (3)	0 (0)	4 (5)	4 (4)	0 (0)	0 (0)	
Unilateral	19 (7)	1 (4)	4 (5)	7 (7)	3 (9)	1 (8)	0.11 (0.04-0.15)
No	226 (88)	25 (89)	69 (89)	87 (89)	31 (91)	12 (92)	
Not assessed	5 (2)	2 (7)	1 (1)	2 (2)	0 (0)	0 (0)	
Hearing aids	20 (8)	1 (4)	11 (14)	4 (4)	2 (6)	2 (15)	0.16 (0.07-0.22)

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia.
y: years. Findings are presented as N and column %.
a: Cramér's V and bias-corrected 95% confidence intervals based on chi-squared test of independence; it ranges from 0 (no association) to 1 (strong association).

eTable 6: Tympanometry findings of EPIC-PCD participants, overall and by age group (N=216)

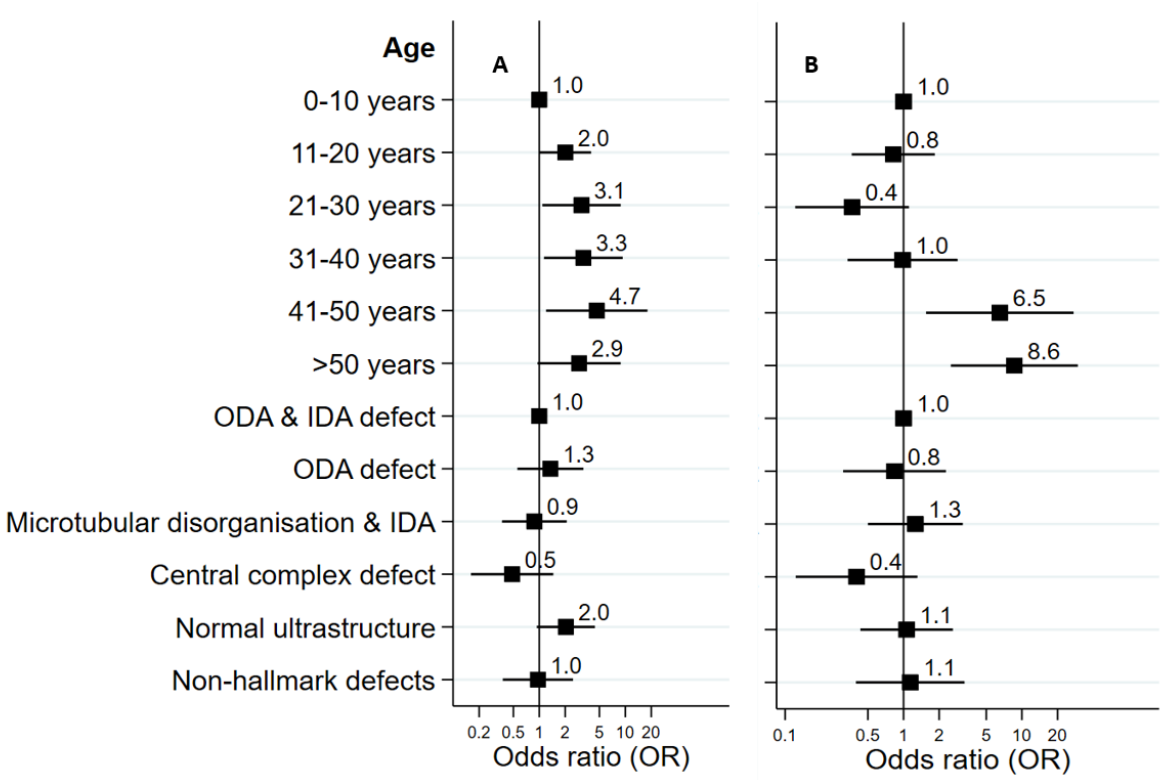
	Total N (%)	Age 0-6 y N (%)	Age 7-14 y N (%)	Age 15-30 y N (%)	Age 31-50 y N (%)	Age >50 y N (%)	Affected ears (N=432) N (%)
Number of participants	216 (100)	14 (100)	70 (100)	92 (100)	26 (100)	14 (100)	
Tympanogram type							
Type A							
Bilateral	72 (32)	3 (21)	19 (27)	43 (47)	9 (34)	0 (0)	180 (41)
Unilateral	36 (16)	2 (14)	9 (13)	16 (25)	7 (27)	4 (29)	
Type B							
Bilateral	91 (42)	6 (43)	38 (54)	28 (30)	11 (42)	8 (57)	205 (47)
Unilateral	23 (11)	1 (7)	5 (7)	7 (8)	2 (8)	4 (29)	
Type C							
Bilateral	19 (9)	3 (21)	4 (6)	8 (9)	1(4)	1 (7)	53 (12)
Unilateral	15 (7)	0 (0)	4 (6)	3 (3)	1(4)	2 (14)	

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia. y: years. Tympanogram types by Jerger; types AD and AS are grouped under type. Findings are presented as N and column %; categories are not exclusive.



eFigure 3 Parts A-B Factors associated with the A) ear inflammation and B) hearing score among EPIC-PCD participants with definite PCD diagnosis

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia
Definite PCD defined as biallelic pathogenic mutation or hallmark defect identified by transmission electron microscopy
For the ear inflammation score, we included any reported ear pain or ear discharge, presence of tympanostomy tubes, otitis media and tympanic perforation during otoscopy, each of which scored as 0 (absence) or 1 (presence); total score ranged from 0 to 4. For the hearing score, we included reported hearing problems (0 to 4: never to daily) and audiometry results (0 to 4: normal to profound hearing impairment) with total score ranging from 0 to 8.



eFigure 4 Parts A-B Association of ciliary ultrastructural defect with the A) ear inflammation and B) hearing score among EPIC-PCD participants

EPIC-PCD: Ear-nose throat prospective international cohort of patients with primary ciliary dyskinesia
For the ear inflammation score, we included any reported ear pain or ear discharge, presence of tympanostomy tubes, otitis media and tympanic perforation during otoscopy, each of which scored as 0 (absence) or 1 (presence); total score ranged from 0 to 4. For the hearing score, we included reported hearing problems (0 to 4: never to daily) and audiometry results (0 to 4: normal to profound hearing impairment) with total score ranging from 0 to 8. Non-hallmark defects include all other class 2 ciliary ultrastructural defects besides central complex defect