Radiology

Low-Dose CT–derived Bronchial Parameters in Individuals with Healthy Lungs

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Conflicts of interest are listed at the end of this article.

See also the editorial by Emrich and Varga-Szemes in this issue.

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Background: CT-derived bronchial parameters have been linked to chronic obstructive pulmonary disease and asthma severity, but little is known about these parameters in healthy individuals.

Purpose: To investigate the distribution of bronchial parameters at low-dose CT in individuals with healthy lungs from a Dutch general population.

Materials and Methods: In this prospective study, low-dose chest CT performed between May 2017 and October 2022 were obtained from participants who had completed the second-round assessment of the prospective, longitudinal Imaging in Lifelines study. Participants were aged at least 45 years, and those with abnormal spirometry, self-reported respiratory disease, or signs of lung disease at CT were excluded. Airway lumens and walls were segmented automatically. The square root of the bronchial wall area of a hypothetical airway with an internal perimeter of 10 mm (Pi10), luminal area (LA), wall thickness (WT), and wall area percentage were calculated. Associations between sex, age, height, weight, smoking status, and bronchial parameters were assessed using univariable and multivariable analyses.

Results: The study sample was composed of 8869 participants with healthy lungs (mean age, 60.9 years ± 10.4 [SD]; 4841 [54.6%] female participants), including 3672 (41.4%) never-smokers and 1197 (13.5%) individuals who currently smoke. Bronchial parameters for male participants were higher than those for female participants (Pi10, slope [β] range = 3.49–3.66 mm; LA, β range = 25.40–29.76 mm^2; WT, β range = 0.98–1.03 mm; all P < .001). Increasing age correlated with higher Pi10, LA, and WT (r^2 range = 0.06–0.09, 0.02–0.01, and 0.02–0.07, respectively; all P < .001). Never-smoking individuals had the lowest Pi10 followed by formerly smoking and currently smoking individuals (3.62 mm ± 0.13, 3.68 mm ± 0.14, and 3.70 mm ± 0.14, respectively; all P < .001). In multivariable regression models, age, sex, height, weight, and smoking history explained up to 46% of the variation in bronchial parameters.

Conclusion: In healthy individuals, bronchial parameters differed by sex, height, weight, and smoking history; male sex and increasing age were associated with wider lumens and thicker walls.

Supplemental material is available for this article.

Chronic respiratory diseases are among the top 10 causes of death worldwide (1). Early diagnosis combined with proactive management of chronic obstructive pulmonary disease is being explored as one method to reduce the associated morbidity and mortality rates (2). Although smoking cessation remains central to treatment of chronic obstructive pulmonary disease, other therapeutic interventions are aimed at reducing symptoms and improving quality of life. For both early detection with timely smoking cessation and monitoring of treatment response, CT-derived bronchial parameters could play a key role (3–5).

Bronchial parameters at CT have been linked to respiratory disease severity and progression in symptomatic patients across a variety of respiratory illnesses, including chronic obstructive pulmonary disease, asthma, and interstitial lung disease (6–10). However, underlying physiologic differences with respect to sex and age may contribute to bronchial parameter variation (11,12). For their potential use as a screening or diagnostic tool, it is important to consider the distribution and range of these parameters in the target population. Currently, most large-scale analyses of bronchial parameters have been conducted in individuals who smoke or patients with chronic obstructive pulmonary disease, with only limited data in individuals who do not currently smoke (13). Most of the insights into bronchial parameters in healthy individuals originate from small groups of healthy control participants who, due to study design and requirements, may not represent the healthy general population, with conflicting results for normal values of bronchial parameters (13). Furthermore, reference values for individuals with healthy lungs from general populations have not been well established.

Abbreviations

ImaLife = Imaging in Lifelines, LA = luminal area, LR = lumen radius, Pi10 = square root of the bronchial wall area of a hypothetical airway with an internal perimeter of 10 mm, TR = total radius, WT = wall thickness

Summary

This prospective study of 8869 individuals with healthy lungs found bronchial parameter measurements were influenced by sex, age, height, weight, and smoking history.

Key Results

- In this prospective study including 8869 participants with healthy lungs, male participants had higher values for three low-dose CT bronchial parameters than female participants (mean square root of the bronchial wall area of a hypothetical airway with an internal perimeter of 10 mm [Pi10], 3.66 mm ± 0.14 vs 3.49 mm ± 0.13; mean luminal area, 29.76 mm^2 ± 5.79 vs 25.40 mm^2 ± 4.66; mean wall thickness, 1.03 mm ± 0.05 vs 0.98 mm ± 0.05; all $P < .001$).
- Age, sex, height, weight, and smoking history contributed to explained variation in bronchial parameters (Pi10: adjusted $R^2 = 0.465$; $P < .001$).

The aim of this study was to examine the distribution of low-dose CT–derived bronchial parameters in individuals with healthy lungs from a Dutch general population.

Materials and Methods

In this prospective study, imaging analysis was performed on data from 12 041 participants from the Imaging in Lifelines (ImaLife) study (14), which was approved by the local medical ethics committee (University Medical Center Groningen) and is registered with the Dutch Central Committee on Research Involving Human Subjects (*https://www.toetsingonline.nl*; identifier: NL58592.042.16). All participants gave informed consent before participation.

Study Design and Participants

ImaLife is part of the Lifelines multidisciplinary prospective population-based three-generation cohort study examining the health and health-related behaviors of 167 729 persons living in the three northern provinces in the Netherlands (14). The ImaLife study focuses on imaging biomarkers for the general population from low-dose CT scans. That study includes participants aged 45 years and older who completed a lung function test during the second-round assessment of the Lifelines study and who were invited to undergo low-dose chest CT between May 2017 and October 2022. The full study design was published previously (15) and includes participant recruitment and sample size estimation. Previous analyses of ImaLife participants are listed in Table S1. Because the focus of the current study was on individuals with healthy lungs, participants with self-reported history of pulmonary disease, medication use for respiratory disease, or abnormal spirometry according to the lower limit of normal for percent predicted forced expiratory volume in 1 second of expiration or forced expiratory volume in 1 second of expiration to forced vital capacity ratio were excluded (Appendix S1). Participants with CT features of respiratory disease, such as interstitial lung disease, emphysema, bronchiectasis, and infection, and those with inadequate airway segmentation were also excluded from the study. Details of lung findings at CT leading to exclusion are described in Appendix S1. Participants were split into groups based on their smoking history (ie, never, former, and current), and their bronchial parameters were measured and analyzed, consisting of the square root of the bronchial wall area of a hypothetical airway with an internal perimeter of 10 mm (Pi10), luminal area (LA), wall thickness (WT), and wall area percentage.

Definitions of Terms

Never smoking was defined as a 0 pack-years history, *former smoking* as self-reported quitting smoking without restarting smoking, and *current smoking* as self-reported smoking within the last month of answering the questionnaire and not reporting having quit smoking.

Image Acquisition and Reconstruction

Each participant underwent a supine inspiratory chest CT examination based on a low-dose noncontrast volumetric scan protocol, using a third-generation dual-source CT scanner (Somatom Force; Siemens Healthineers). For scan reconstruction, a hard Qr59 kernel that was designed for quantitative purposes was used with section thickness of 1 mm and section increment of 0.7 mm.

Image Analysis

Scans were automatically processed to calculate bronchial parameters. The airway lumen was extracted using a three-dimensional U-Net as previously described (16). Next, the airway lumen was refined and the outer wall segmented using an optimal-surface graph-cut method (17). This in-house pipeline *(https://github.com/id-b3/AirFlow-ImaLife)* was validated previously in a representative sample of the ImaLife data set with good reproducibility (18). Segmentations were automatically flagged for review when unusually low or high lung volume, airway volume, airway count, or rapid radius changes indicated potential segmentation errors. The segmentations flagged for review were combined with a random sample of nonflagged segmentations for a total of 2000 segmentations reviewed by a medical doctor (I.D., with 3 years of experience in airway segmentation research and evaluation and experience in radiology and pulmonology departments) who was blinded to participant characteristics. A three-point Likert scale was used to evaluate quality for leaks, segmentation completeness, and segmentation extent (Appendix S2).

Several bronchial parameters were calculated from measurements of the lumen and total radii taken every 0.5 mm along the centerline of the airway segmentation. The average of these measurements per branch was used to calculate the lumen radius (LR) and total radius (TR). LR and TR were used to calculate the following parameters: $LA = \pi(LR)^2$; $WT = TR - LR$; and $WAP = [(TA - LA)/TA]100$, where WAP is wall area percentage and TA is total area, calculated as $\pi(TR)^2$. Pi10 was calculated using airways from generation zero (trachea) through six. The sixth airway generation was chosen as a threshold based on the robustness of airway measurements (19). The square root of the bronchial wall area was plotted against the internal perimeter per branch, and a robust regression line was calculated (19). Pi10 was measured at the intercept for an internal perimeter of 10 mm (Fig S1).

LA, WT, and wall area percentage were averaged across airway generations three through five (20).

Statistical Analyses

The Student *t* test was used to compare group means by sex with Bonferroni correction for multiple comparisons. One-way analysis of variance with the Tukey honest significant difference post hoc test was used to assess means across groups based on smoking history. Percentiles (10th–90th) for each bronchial parameter were determined for sex and smoking status using 5-year age categories.

To examine the strength and direction of relationships between age, height, weight, and bronchial parameters, univariable linear regression was performed, and the slope (β) and coefficient of determination (r^2) were calculated. Additionally, multivariable linear regression models were created for each bronchial parameter incorporating the independent variables sex, age, height, weight, smoking status, and pack-years. The

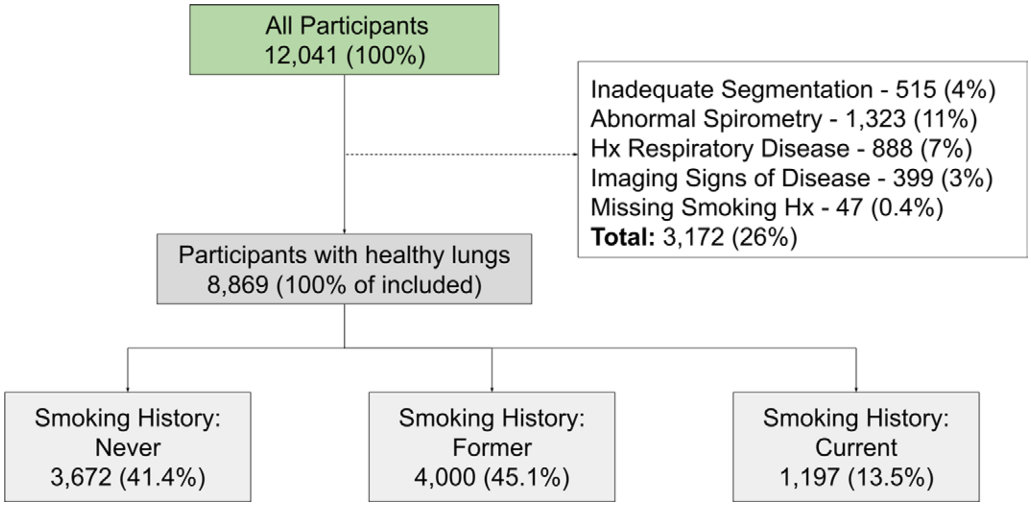

Figure 1: Flowchart of participant inclusion and exclusion and group division. Hx = history.

Table 1: Participant Characteristics

Parameter	Total (*n* = 8869)	Male Participants	Female Participants	*P* Value
Age (y)	60.9 ± 10.4	61.7 ± 10.8	60.2 ± 10.1	<.001
Height (m)	1.74 ± 0.09	1.81 ± 0.07	1.68 ± 0.06	<.001
Weight (kg)	79.7 ± 14.1	86.8 ± 12.4	73.7 ± 12.5	<.001
BMI	26.18 ± 3.81	26.37 ± 3.27	26.02 ± 4.19	<.001
Smoking history (no. of patients)				
Never	3672 (41.4)	1562 (42.5)	2110 (57.5)	…
Former	4000 (45.1)	1852 (46.3)	2148 (53.7)	…
Current	1197 (13.5)	614 (51.3)	583 (48.7)	…
Pack-years*				
Total	11.8 ± 10.8	13.9 ± 11.9	9.8 ± 9.2	<.001
Former	10.4 ± 9.7	12.7 ± 11.3	8.1 ± 8.1	<.001
Current	16.9 ± 11.5	17.8 ± 12.6	16.1 ± 10.3	.012
FEV_1 (L)	3.30 ± 0.78	3.89 ± 0.68	2.83 ± 0.48	<.001
FEV_1 PP (%)	100 ± 12	100 ± 13	100 ± 12	.77
FVC (L)	4.34 ± 1.01	5.13 ± 0.85	3.69 ± 0.61	<.001
FEV_1/FVC	0.76 ± 0.05	0.76 ± 0.05	0.77 ± 0.05	<.001
TLV (L)	5.4 ± 1.2	6.1 ± 1.2	4.7 ± 0.8	<.001
Pi10 (mm)	3.57 ± 0.16	3.66 ± 0.14	3.49 ± 0.13	<.001
LA (mm^2)	27.38 ± 5.64	29.76 ± 5.79	25.40 ± 4.66	<.001
WT (mm)	1.00 ± 0.05	1.03 ± 0.05	0.98 ± 0.05	<.001
Wall area percentage (%)	47.25 ± 3.36	46.96 ± 3.42	47.50 ± 3.29	<.001

Note.—Except where indicated, data are means ± SDs. Data in parentheses are percentages. *P* values are for *t* test comparisons between male and female participants. BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LA = luminal area, Pi10 = square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm, PP = percent predicted, TLV = total lung volume, WT = wall thickness.

* Individuals who never smoked were not included in calculating the mean pack-years. α = .0038 for significance after Bonferroni correction.

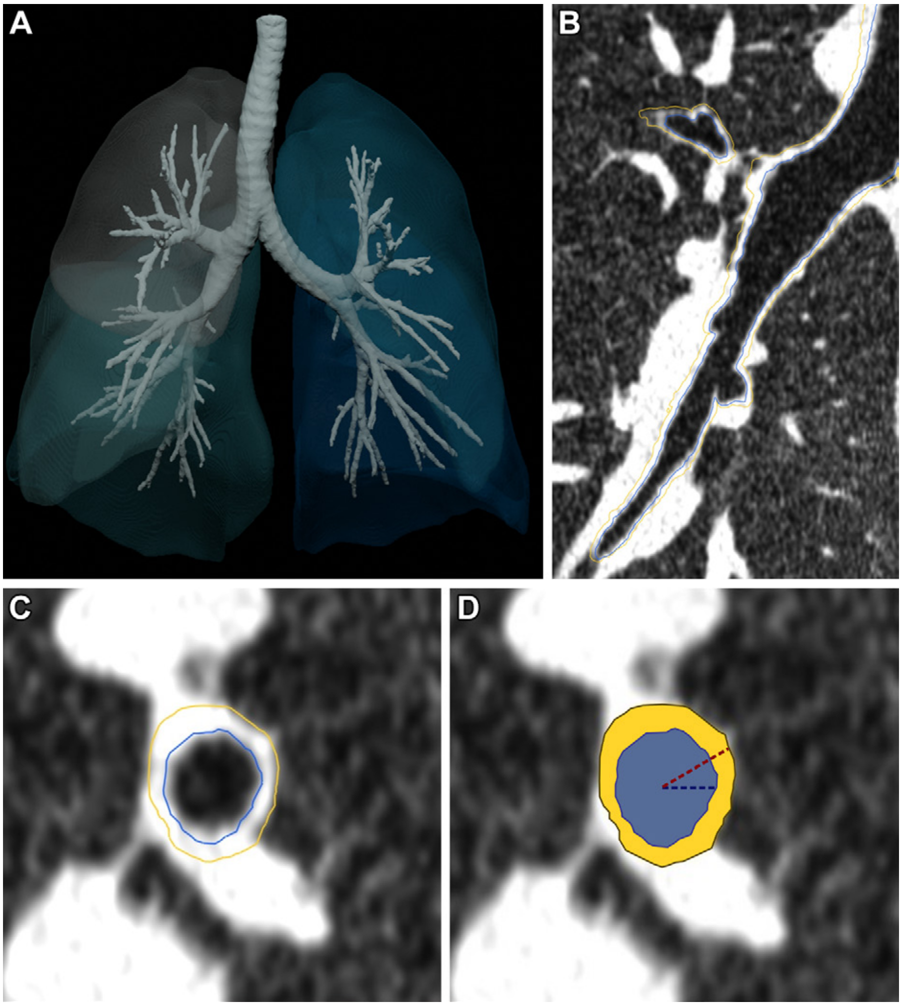

Figure 2: **(A)** Three-dimensional rendering of an exemplary airway segmentation. **(B)** Coronal view of a low-dose CT example of airway lumen and wall segmentation along the length of an airway (yellow outline). **(C)** Multiplanar reconstructed low-dose CT section perpendicular to the airway center line demonstrates the airway lumen (blue outline) and wall (yellow outline) segmentation boundaries. **(D)** Example measurements of lumen radius (blue dashed line) and total radius (red dashed line). These measurements are obtained every 0.5 mm along the center line of the airway. They are used to calculate the rest of the bronchial parameters: the luminal area (blue region) and wall area (yellow region).

adjusted R^2 was used to investigate explained variance for each multivariable model. To assess feature importance, independent variables were normalized, and the absolute value of the resulting coefficients was visualized for each model. Last, equations for calculating reference bronchial parameters were derived and adjusted for sex, age, height, weight, smoking status, and pack-years. The threshold for significance (α) was indicated by .05. When Bonferroni correction was used, the threshold for significance was indicated by .0038. Statistical analyses were performed (I.D.) using SciPy and Statsmodels (Python, version 3.10; Python Software Foundation).

Results

Participant Characteristics

Of 12 041 participants, 1323 were excluded for abnormal spirometry, 888 for history of respiratory disease, 399 for imaging features of respiratory illness, 47 for missing smoking data, and 515 for inadequate bronchial segmentation (Fig 1). A total of 8869 participants (mean age, 60.9 years ± 10.4 [SD]; 4841 [54.6%] female participants, 4028 [45.4%] male participants) were included; 3672 (41.4%), 4000 (45.1%), and 1197 (13.5%) were never smoking, formerly smoking, and currently smoking, respectively (Table 1). The mean pack-years were 16.9 pack-years ± 11.5 for individuals who currently smoked and 10.4 pack-years ± 9.7 for individuals who formerly smoked. Height (mean, 1.81 m ± 0.07 vs 1.68 m ± 0.06; $P < .001$), weight (mean, 86.8 kg ± 12.4 vs 73.7 kg ± 12.5; $P < .001$), smoking pack-years (mean, 13.9 pack-years ± 11.9 vs 9.8 pack-years ± 9.2; $P < .001$), and total lung volume (mean, 6.1 L ± 1.2 vs 4.7 L ± 0.8; $P < .001$) were greater in male participants than in female participants, respectively. Exemplary segmentation of airway tree, lumen, and wall borders is shown in Figure 2.

Visual scoring of the random sample of scans from the included participants showed a mean quality of 2.86 ± 0.43 for leaks, 2.86 ± 0.44 for completion, and 2.63 ± 0.59 for extent (Fig S2).

Bronchial Parameter Distribution and Percentile Values

Pi10, LA, and WT were larger and wall area percentage was smaller in male participants compared with female participants ($P < .001$; Table 1). These sex differences were still observed when stratified by smoking status (Table S2). Bronchial parameters are provided as percentile values per age category in Table 2 by sex. Generally, it was observed that with increasing age, Pi10 and WT increased and the LA widened. Furthermore, it was observed that wall area percentage decreased until age 65–70 years, when it began to increase again. These observations were also observed when male participants and female participants were categorized as individuals who never smoked (Table S3) and individuals who currently smoke (Table S4).

Univariable Analysis Assessing Relationships between Participant Characteristics and Bronchial Parameters

For both sexes, univariable linear regression analysis showed a positive but weak correlation of age, weight, and body mass index (calculated as weight in kilograms divided by height in meters squared) with Pi10 (β range, 0.01–0.04; r^2 range, 0.06–0.13; $P < .001$) (Table 3). Although a small change in

Table 2: Reference Bronchial Parameter Percentiles Split by Age and Sex

	Age (y)							
Parameter	45–49	50–54	55–59	60–64	65–69	70–74	75–79	≥80
Male participants								
No. of male participants	540	637	738	646	422	352	392	300
Pi10								
10th percentile	3.45	3.48	3.47	3.48	3.51	3.50	3.54	3.53
25th percentile	3.52	3.55	3.56	3.56	3.59	3.60	3.62	3.64
50th percentile	3.60	3.63	3.64	3.65	3.69	3.69	3.70	3.73
75th percentile	3.70	3.72	3.74	3.75	3.79	3.79	3.82	3.83
90th percentile	3.76	3.81	3.83	3.83	3.87	3.87	3.89	3.90
WT								
10th percentile	0.96	0.97	0.97	0.97	0.98	0.97	0.98	0.98
25th percentile	0.99	1.00	1.00	1.00	1.01	1.00	1.01	1.01
50th percentile	1.02	1.03	1.03	1.03	1.04	1.04	1.04	1.05
75th percentile	1.05	1.05	1.06	1.06	1.07	1.07	1.07	1.08
90th percentile	1.08	1.08	1.09	1.08	1.09	1.10	1.10	1.10
LA								
10th percentile	21.94	21.78	22.69	22.86	23.07	23.25	23.26	22.93
25th percentile	25.01	24.99	25.91	25.77	26.35	26.54	26.40	25.70
50th percentile	28.03	28.42	29.19	30.03	29.97	30.06	30.40	29.99
75th percentile	31.34	32.45	33.33	33.64	34.27	34.08	34.67	34.95
90th percentile	35.18	36.52	36.99	37.74	38.23	37.42	38.71	39.22
Wall area percentage								
10th percentile	43.36	43.11	42.87	42.22	42.40	42.66	42.11	41.84
25th percentile	45.29	45.24	44.59	44.29	44.33	44.37	43.94	44.28
50th percentile	47.53	47.26	46.86	46.43	46.71	46.67	46.54	46.76
75th percentile	49.65	49.65	48.97	48.98	48.85	49.04	49.06	49.62
90th percentile	51.60	51.82	51.52	51.29	51.03	51.02	51.22	51.99
Female participants								
No. of participants	756	836	944	742	557	418	390	197
Pi10								
10th percentile	3.32	3.31	3.32	3.31	3.32	3.35	3.39	3.41
25th percentile	3.37	3.38	3.38	3.38	3.40	3.43	3.47	3.51
50th percentile	3.45	3.45	3.47	3.47	3.49	3.52	3.58	3.61
75th percentile	3.52	3.53	3.56	3.56	3.59	3.61	3.66	3.71
90th percentile	3.59	3.61	3.65	3.65	3.67	3.70	3.73	3.76
WT								
10th percentile	0.92	0.91	0.92	0.92	0.93	0.93	0.95	0.95
25th percentile	0.94	0.94	0.94	0.94	0.95	0.96	0.98	0.98
50th percentile	0.97	0.97	0.97	0.97	0.98	0.99	1.01	1.02
75th percentile	1.00	1.00	1.01	1.01	1.01	1.02	1.03	1.04
90th percentile	1.02	1.02	1.04	1.04	1.04	1.05	1.06	1.07
LA								
10th percentile	18.81	19.53	19.97	19.84	20.24	20.20	19.95	19.62
25th percentile	20.92	21.88	22.27	22.64	23.00	22.87	22.59	22.18
50th percentile	23.85	24.72	25.25	25.55	26.01	25.77	25.70	25.44
75th percentile	26.92	27.87	28.22	28.76	29.29	28.92	28.88	27.95
90th percentile	29.55	30.82	31.24	32.17	32.99	32.32	32.42	32.07
Wall area percentage								
10th percentile	44.22	43.56	43.47	42.99	42.58	42.87	43.60	44.00
25th percentile	46.00	45.27	45.13	44.70	44.63	44.91	45.56	46.41
50th percentile	48.06	47.50	47.24	46.77	46.83	47.03	47.58	48.03
75th percentile	50.32	49.68	49.60	49.47	49.19	49.62	49.94	50.75
90th percentile	52.20	51.43	51.69	51.71	51.20	51.83	51.83	52.93

Note.—Data are percentile values. LA = luminal area, Pi10 = square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm, WT = wall thickness.

Table 3: Univariable Linear Regression and Correlation Analysis for Bronchial Parameters with Participant Characteristics

	Age			Height			Weight			BMI		
Parameter	β*	r^2 Value	*P* Value	β	r^2 Value	*P* Value	β*	r^2 Value	*P* Value	β	r^2 Value	*P* Value
Male participants												
Pi10	0.03	0.06	<.001	0.08	0	.02	0.04	0.12	<.001	0.02	0.13	<.001
WT	0.01	0.02	<.001	−0	0	.7	0.01	0.12	<.001	0.01	0.16	<.001
LA	0.68	0.02	<.001	11.5	0.02	<.001	−0.37	0.01	<.001	−0.31	0.03	<.001
Wall area percentage	−0.22	0.01	<.001	−4.92	0.01	<.001	0.58	0.04	<.001	0.32	0.09	<.001
Female participants												
Pi10	0.04	0.09	<.001	−0.08	0	.004	0.03	0.07	<.001	0.01	0.1	<.001
WT	0.01	0.07	<.001	−0.04	0	<.001	0.01	0.09	<.001	0.01	0.13	<.001
LA	0.56	0.01	<.001	10.7	0.02	<.001	−0.26	0	<.001	−0.16	0.02	<.001
Wall area percentage	−0.1	0	.03	−6.56	0.02	<.001	0.49	0.03	<.001	0.2	0.06	<.001

Note.—β = slope, BMI = body mass index (calculated as weight in kilograms divided by height in meters squared), LA = luminal area, Pi10 = square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm, WT = wall thickness.

* Per 10-unit increase.

Table 4: Multivariable Linear Regression Analysis for Bronchial Parameters

	Pi10 (mm)			WT (mm)			LA (mm^2)			Wall Area Percentage		
Parameter	$β_1$	R^2 Value	*P* Value	$β_1$	R^2 Value	*P* Value	$β_1$	R^2 Value	*P* Value	$β_1$	R^2 Value	*P* Value
Overall model		0.465	<.001		0.412	<.001		0.207	<.001		0.104	<.001
Sex	0.12		<.001	0.037		<.001	2.38		<.001	0.08		.41
Age (y)*	0.043		<.001	0.01		<.001	0.91		<.001	−0.27		<.001
Height (m)	0.008		.002	−0.07		<.001	20.23		<.001	−12.46		<.001
Weight (kg)*	0.04		<.001	0.015		<.001	−0.59		<.001	0.73		<.001
Smoking history, current	0.041		<.001	0.015		<.001	−0.11		.55	0.49		<.001
Pack-years												
1–10	0		.56	0		.75	0.09		.48	−0.04		.63
10–20	0.017		<.001	0.007		<.001	0.13		.43	0.21		.045
>20	0.059		<.001	0.021		<.001	−0.12		.57	0.79		<.001

Note.—The adjusted R^2 values and *F* statistic *P* values are shown for the overall model. For each independent variable, the coefficients are shown with their corresponding *P* values. β = slope, LA = luminal area, Pi10 = square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm, WT = wall thickness.

* Per 10-unit increase.

Pi10 for a unit increase in height was shown, there was no evidence that one variable explained the other for male and female participants (β = 0.08, −0.08; r^2 = 0; *P* = .02, .004, respectively). There was a weak positive correlation of age, weight, and body mass index with WT for both sexes (β = 0.01; r^2 range = 0.02–0.16).

For both sexes, age and height displayed a weak positive correlation with LA (β range = 0.56–11.5; r^2 range = 0.01–0.02), while weight and body mass index were negatively correlated (β range = −0.37 to −0.16; r^2 range = 0.0–0.03). This result was reversed for wall area percentage (β range = −6.56 to −0.1, r^2 range = 0.0–0.02 for age and height; β range = 0.2–0.58, r^2 range = 0.03–0.09 for weight and body mass index).

Comparing bronchial parameters between participants stratified by smoking history, individuals who never smoked had lower values for Pi10 versus former and current smokers (Pi10: 3.62 mm ± 0.13, 3.68 mm ± 0.14, and 3.70 mm ± 0.14 for never, former, and current smoking male participants, respectively; 3.47 mm ± 0.13, 3.49 mm ± 0.13, and 3.53 mm ± 0.14 for never, former, and current smoking female participants, respectively; *P* < .001 for all comparisons; Table S2). In male participants who formerly smoked, the LA value was larger than that in current smokers (LA mean difference, 0.863 mm^2; *P* = .004; Table S5).

Multivariable Analysis and Reference Bronchial Parameter Equations

The multivariable linear regression model for each bronchial parameter showed a good fit based on the overall *F* statistic (*P* < .001). Multivariable linear models for Pi10 and WT achieved an adjusted R^2 of 0.465 and 0.412, respectively, whereas those for LA and wall area percentage achieved an adjusted R^2 of 0.207 and 0.104, respectively (Table 4). Sex was correlated with a change in Pi10 (β_1 = 0.12; $P < .001$), LA (β_1 = 2.38; $P < .001$), and WT (β_1 = 0.037; $P < .001$), but no evidence of a correlation with a change in wall area percentage was observed (β_1 = 0.08; $P = .41$).

All parameters increased with age except for wall area percentage, which decreased (β_1 = −0.27% per 10 years; $P < .001$). Height was related to increased Pi10 and LA and decreased WT and wall area percentage (β_1 = 0.008 mm, 20.23 mm^2, −0.07 mm, and −12.46%, respectively; $P = .002$ for Pi10; $P < .001$ for LA, WT, and wall area percentage). Weight correlated with increased Pi10, WT, and wall area percentage and decreased LA (β_1 = 0.04, 0.015, 0.73, and −0.59, respectively; all $P < .001$).

Current smoking was related to increased Pi10 (β_1 = 0.041; $P < .001$), WT (β_1 = 0.015; $P < .001$), and wall area percentage (β_1 = 0.49; $P < .001$), but no evidence of a relationship with LA was observed (β_1 = −0.11; $P = .55$). A history of more than 10 pack-years was related to increased Pi10, WT, and wall area percentage but had no evidence of an effect on LA. Based on feature importance analysis, it was observed that age, height, and weight together accounted for 80% or more of the explained variance for each bronchial parameter, and smoking history had an overall influence of less than 20% (Fig 3).

For each bronchial parameter, the model coefficients were used to derive a normalized reference parameter equation, accessible as an online calculator at *https://www.b3care.nl/bp_calc/* and in Figure S3 and Appendix S3.

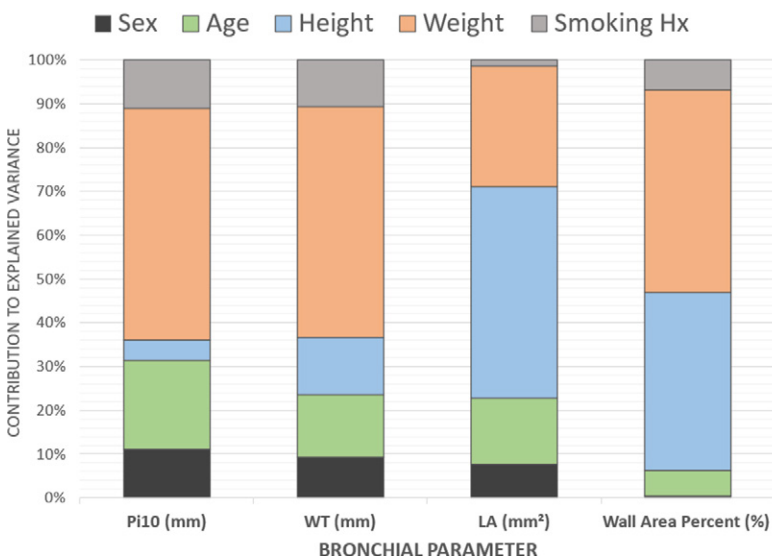

Figure 3: Stacked bar plot shows the feature importance of independent variables for each bronchial parameter. Feature importance was calculated using the coefficients of the independent variables sex, age, height, weight, and combined smoking history from normalized multivariable linear regression models for each of the bronchial parameters. Hx = history, LA = luminal area, Pi10 = square root of the wall area of a hypothetical airway with an internal perimeter of 10 mm, WT = wall thickness.

Discussion

To determine the distribution and influencing factors of bronchial parameters in individuals with normal lung function, we measured the airways of 8869 participants of the Imaging in Lifelines study. We found that male participants had thicker bronchial walls and wider bronchial lumens than female participants (wall thickness [WT]: 1.03 mm ± 0.05 vs 0.98 mm ± 0.05, $P < .001$; luminal area [LA]: 29.76 mm^2 ± 5.79 vs 25.40 mm^2 ± 4.66, $P < .001$), and this difference remained after accounting for age, height, weight, and smoking status. With aging, there was a small but steady increase in WT (β = 0.01 mm per 10 years; $P < .001$) and LA (β = 0.91 mm^2 per 10 years; $P < .001$), which was also reflected in a higher square root of the bronchial wall area of a hypothetical airway with an internal perimeter of 10 mm (β = 0.043 mm per 10 years; $P < .001$).

Previous studies that investigated CT-derived bronchial parameters in a healthy group have included healthy individuals primarily as a control group for respiratory disease cohorts (13). These studies report inconsistent findings regarding bronchial parameters, with some suggesting thinner airway walls in male participants (12) and others showing thicker walls (11,21,22) or no difference (23). However, our study in a much larger cohort of 8869 individuals with healthy lungs from the general population now provides evidence that men have higher wall thickness compared with women, even when accounting for age, height, weight, and smoking history. The discrepancies observed in previous studies may be attributed to the variation in method, scale, and differential impact of physical characteristics on different bronchial parameters (13). Our analysis revealed that sex, age, height, weight, and smoking history explain some of the variation in wall area percentage and LA (R^2 range = 0.104–0.207; $P < .001$) and accounted for almost half of the explained variation of the WT and Pi10 distributions (R^2 range = 0.412–0.465; $P < .001$).

Aging was related to small increases in LA and WT, resulting in an increased Pi10, but showed no evidence of an influence on wall area percentage. The increase in LA could be due to parenchymal changes of the aging lung, namely loss of elasticity (24,25) and reduction in density (26,27). This change in increased airspace has been noted on histology and micro-CT of donor lungs (28). The findings are similar to a recent investigation (29) of the aging airway morphologic structure in 431 participants who never smoked, which found an LA increasing with aging in male participants. Although the authors did not find the same association in female participants, our findings in a larger study sample support that age-related changes are present in both sexes. This result has also been observed in a past study; however, the study sample was primarily heavy smokers recruited for a lung cancer screening trial (30). Moreover, we found that height and weight exerted an influence on bronchial parameters. Height demonstrated a positive correlation with Pi10 and LA. Meanwhile, weight exhibited positive associations with Pi10, WT, and wall area percentage but showed a negative correlation with LA. The results reinforce the importance of considering sex, age, and height in the evaluation of bronchial parameters.

This study had several limitations. First, the study sample examined in the ImaLife study represents a specific population from the northern provinces of the Netherlands, primarily composed of White individuals who were taller compared with most countries. Second, the segmentation methods and scan protocols used may influence bronchial parameters, which may have contributed to potential inconsistencies in comparisons between studies. Last, the nonsystematic nature of the image review beyond lung nodules and emphysema may have resulted in the retention of a small number of participants with undiagnosed or subtle respiratory conditions, particularly if findings at CT were not extensive. This factor should be considered when interpreting the findings.

Bronchial parameters not only provide insights into airway morphologic structure in the context of screening and diagnosis but also have potential therapeutic applications, as shown by their capacity to gauge treatment response in respiratory illnesses after intervention (31–33). Previous research also highlighted bronchial parameters as measures of improvement after smoking cessation in individuals with chronic obstructive pulmonary disease (34,35). However, confounding factors such as sex, age, and height have sometimes been overlooked in studies measuring bronchial parameters. Our findings emphasize the importance of these factors, suggesting their integration could enhance bronchial parameter sensitivity in clinical applications.

Overall, this study examined the distribution of CT-derived bronchial parameters in a large healthy Dutch cohort. In healthy individuals, bronchial parameters differed by sex, height, weight, and smoking history. Male sex and increasing age were associated with wider lumens and thicker walls. The reference equations and percentile values provided in this study could be used as a benchmark for assessing the bronchial parameter for an individual stemming from a population similar to our study sample and identify deviations from normal values. Future research of bronchial parameters is needed in diverse populations in other countries as well as standardization of bronchial parameter calculation methods.

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Author contributions: Guarantors of integrity of entire study, **I.D., M.v.D.B., R.V.**; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, **I.D., G.S., D.J.S., M.v.d.B., R.V.**; clinical studies, **G.J.P., M.v.d.B., R.V.**; experimental studies, **I.D., A.G.U.**; statistical analysis, **I.D., G.J.P., G.S., G.H.d.B.**; and manuscript editing, **I.D., G.J.P., G.S., J.P., D.J.S., G.H.d.B., M.v.d.B., M.d.B., R.V.**

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