



Figure S1 Flow diagram of the study.

Table S1 CT-diagnosed emphysema, medically diagnosed comorbidities (self-reported), respiratory symptoms and use of bronchodilators among LUSI participants classified as having COPD, by GOLD-stages 1, 2, or 3–4, compared to normal spirometry

| Symptoms and comorbidities | COPD, GOLD 1 (n=92) | COPD, GOLD 2 (n=236) | COPD, GOLD 3-4 (n=41) | Normal spirometry (n=1,307) |
|--|---------------------|----------------------|-----------------------|-----------------------------|
| Frequent pulmonary symptoms | | | | |
| Chronic cough | 24 (26.1%); P=0.04 | 70 (29.7%); P<0.01 | 19 (46.3%); P<0.01 | 197 (15.1%) |
| Chronic sputum production | 23 (25.0%); P<0.01 | 60 (25.4%); P<0.01 | 14 (34.1%); P<0.01 | 157 (12.0%) |
| Dyspnea (at rest) | 0 (0.0%); P=0.80 | 8 (3.4%); P=0.05 | 1 (2.4%); P=0.09 | 15 (1.1%) |
| Avoiding physical efforts because of breathlessness | 2 (2.2%); P=1.0 | 21 (8.9%); P<0.01 | 10 (24.4%); P<0.01 | 39 (3.0%) |
| Persistent bronchial infections | 11 (12.0%); P=0.08 | 35 (14.8%); P<0.01 | 7 (17.1%); P<0.01 | 91 (7.0%) |
| Any of the above symptoms | 31 (33.7%); P=0.01 | 105 (44.5%); P<0.01 | 25 (61.0%); P<0.01 | 288 (22.0%) |
| Use of medications | | | | |
| Bronchodilators (inhalers) | 8 (8.7%); P=0.21 | 45 (19.1%); P<0.01 | 15 (36.6%); P<0.01 | 57 (4.4%) |
| Medically diagnosed respiratory disease, self-reported | | | | |
| Chronic bronchitis (ever)* | 13 (14.1%); P=0.33 | 63 (26.7%); P<0.01 | 16 (39.0%); P<0.01 | 119 (9.1%) |
| Chronic bronchitis (past 12 months)** | 1 (0.3%); P=0.34 | 2 (0.8%); P=0.29 | 2 (4.9%); P=0.02 | 5 (0.4%) |
| COPD (past 12 months)** | 1 (1.1%); P=0.34 | 7 (3.0%); P<0.01 | 3 (7.3%); P<0.01 | 5 (0.4%) |
| Emphysema (past 12 months)** | 0 (0.0%); P=1.00 | 3 (1.3%); P=0.01 | 1 (2.4%); P=0.06 | 1 (0.1%) |
| Any of the four diagnoses above | 13 (14.1%); P=0.13 | 67 (28.4%); P<0.01 | 15 (36.6%); P<0.01 | 118 (9.0%) |
| Asthma (ever) * | 2 (2.2%); P=1.00 | 24 (10.2%); P<0.01 | 8 (19.5%); P<0.01 | 37 (2.8%) |
| Prior (ever) diagnosis of other (non-pulmonary) disease or major health events, self-reported | | | | |
| Diabetes | 3 (3.3%); P=0.24 | 20 (8.5%); P=0.97 | 6 (14.6%); P=0.32 | 101 (7.7%) |
| Stroke | 5 (5.4%); P=0.59 | 10 (4.2%); P=0.86 | 5 (12.2%); P=0.03 | 54 (4.1%) |
| Heart attack | 7 (7.6%); P=0.85 | 28 (11.2%); P=0.18 | 3 (7.3%); P=1.00 | 118 (9.0%) |
| Coronary heart disease | 4 (4.3%); P=0.49 | 19 (8.1%); P=0.02 | 1 (2.4%); P=0.08 | 73 (5.2%) |
| Hypertension | 31 (33.7%); P=0.68 | 93 (39.4%); P=0.06 | 17 (41.5%); P=0.20 | 403 (30.8%) |

* Questionnaire at baseline visit (1st screening round); ** Questionnaire at 1st follow-up visit (2nd screening round). GOLD, Global Initiative for chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease, PRISm, preserved ratio impaired spirometry.

Table S2 Basic characteristics* of LUSI screening arm participants with spirometric COPD (n=369), who reported a previous physician's diagnosis of chronic bronchitis, emphysema or COPD ("known disease") or did not report such diagnosis ("unknown disease")

| Characteristics | Known respiratory disease (n=89, 24.1%) | Unknown respiratory disease (n=280, 75.9%) | P value |
|---|--|---|---------|
| FEV ₁ /FVC | 0.64 (0.61); [0.56–0.68] | 0.65 (0.62); [0.60–0.68] | 0.41 |
| FEV ₁ (L) | 2.12 (2.14); [1.68–32.62] | 2.41 (2.38); [1.84–2.90] | <0.01 |
| FEV ₁ % predicted | 63.84 (64.09); [53.49–75.58] | 72.99 (71.24); [62.69–81.90] | <0.01 |
| FVC (L) | 3.48 (3.49); [2.71–4.14] | 3.77 (3.91); [3.13–4.43] | <0.01 |
| FVC% predicted | 81.14 (81.43); [72.99–90.77] | 97.80 (91.37); [79.47–98.16] | <0.01 |
| Age (years) | 58.1 (58.7); [54.9–62.2] | 59.6 (59.4); [54.0–64.5] | 0.27 |
| Sex | | | 0.89 |
| Male | 64 (71.9%) | 197 (70.4%) | |
| Female | 25 (28.1%) | 83 (29.6%) | |
| BMI (kg/m ²) | 24.8 (26.4) [23.6–29.0] | 25.4 (26.0) [23.0–28.0] | 0.42 |
| Smoking status | | | 0.13 |
| Current | 25 (28.1%) | 104 (37.1%) | |
| Former | 64 (71.9%) | 176 (62.9%) | |
| Smoking duration, years | | | 0.19 |
| 26–30 | 9 (10.1%) | 41 (14.6%) | |
| 31–35 | 19 (21.3%) | 73 (26.1%) | |
| 36–40 | 28 (31.5%) | 67 (23.9%) | |
| 41–45 | 27 (30.3%) | 63 (22.5%) | |
| 46–50 | 4 (4.5%) | 29 (10.4%) | |
| >50 | 2 (2.2%) | 7 (2.5%) | |
| Time since quitting, years | | | 0.72 |
| <1 month | 0 (0.0%) | 3 (2.9%) | |
| 1–6 months | 1 (0.4%) | 8 (7.7%) | |
| 7 months–1 year | 1 (0.4%) | 6 (5.8%) | |
| 1–2 years | 5 (20.0%) | 10 (9.6%) | |
| 3–5 years | 8 (3.2%) | 41 (39.4%) | |
| 6–10 years | 10 (40.0%) | 36 (34.6%) | |
| Average daily cigarettes | | | 0.50 |
| 11–15 | 10 (11.2%) | 46 (16.4%) | |
| 16–20 | 28 (31.5%) | 81 (28.9%) | |
| 21–25 | 19 (21.3%) | 60 (21.4%) | |
| 26–30 | 12 (13.5%) | 36 (12.9%) | |
| 31–35 | 5 (5.6%) | 20 (7.1%) | |
| 36–40 | 5 (5.6%) | 21 (7.5%) | |
| 41–45 | 2 (2.2%) | 4 (1.4%) | |
| 46–50 | 3 (3.4%) | 7 (2.5%) | |
| 51–55 | 3 (3.4%) | 5 (1.8%) | |
| 56–60 | 1 (1.1%) | 0 (0.0%) | |
| >60 | 1 (1.1%) | 0 (0.0%) | |
| Education ^b | | | 0.90 |
| Primary/lower secondary [ISCED 1–2] | 41 (46.0%) | 133 (47.5%) | |
| Secondary [ISCED 3] | 22 (24.7%) | 68 (24.3%) | |
| Post secondary/non tertiary [ISCED 4] | 7 (7.9%) | 22 (7.9%) | |
| Tertiary (university level) [ISCED 5/6] | 18 (20.2%) | 53 (18.9%) | |
| Other/unknown | 1 (1.1%) | 4 (1.5%) | |
| Higher education | 19 (21.3%) | 57 (20.4%) | 0.85 |
| Chronic cough | 46 (51.7%) | 67 (23.9%) | <0.01 |
| Chronic sputum production | 39 (43.8%) | 58 (20.7%) | <0.01 |
| Dyspnea (at rest) | 6 (6.7%) | 3 (1.1%) | 0.01 |
| Avoiding physical efforts because of breathlessness | 17 (19.1%) | 16 (5.7%) | <0.01 |
| Persistent bronchial infections | 31 (34.8%) | 22 (7.9%) | <0.01 |
| Any of the above symptoms | 65 (73.0%) | 96 (34.3%) | <0.01 |

* , median (mean) values and IQR ranges [in square brackets] are reported for continuous variables, while n (%) are reported for categorical variables; ^b , German denomination of formal education level: Volks/Hauptschulabschluss [ISCED 1–2], Mittlere Reife [ISCED 3], Fachhochschule [ISCED 4], Hochschule [ISCED 5/6]. P values: for continuous variables these are derived using independent t-test, while for the categorical ones, the Fisher's exact test was used. FEV₁, forced expiration in one second; FVC, forced vital lung capacity; BMI, body mass index; ISCED, International Standard Classification of Education.

Table S3 Basic characteristics* of LUSI screening arm participants with spirometric PRISm (n=311), who reported a previous physician's diagnosis of chronic bronchitis, emphysema or COPD ("known disease") or did not report such diagnosis ("unknown disease")

| Characteristics | Known respiratory disease (n=89, 24.1%) | Unknown respiratory disease (n=280, 75.9%) | P value |
|---|--|---|---------|
| FEV ₁ /FVC | 0.78 (0.79) [0.74-0.83] | 0.78 (0.79) [0.74-0.83] | 0.96 |
| FEV ₁ (L) | 2.20 (2.26) [1.84-2.55] | 2.34 (2.36) [1.99-2.73] | 0.21 |
| FEV ₁ % predicted | 71.47 (69.21) [63.50-75.10] | 74.82 (72.44) [68.98-77.24] | 0.05 |
| FVC (L) | 2.74 (2.87) [2.29-3.34] | 2.96 (3.01) [2.49-3.45] | 0.21 |
| FVC% predicted | 68.81 (69.03) [62.35-76.77] | 72.74 (72.03) [66.94-78.38] | 0.02 |
| Age (years) | 54.4 (56.3) [52.1-58.9] | 57.1 (58.0) [52.7-62.0] | 0.04 |
| Sex | | | 0.18 |
| Male | 28 (50.9%) | 156 (60.9%) | |
| Female | 27 (49.1%) | 100 (39.1%) | |
| BMI (kg/m ²) | 26.9 (28.3) [24.4-31.7] | 26.9 (27.5) [24.6-30.1] | 0.31 |
| Smoking status | | | 0.02 |
| Current | 43 (78.2%) | 158 (61.7%) | |
| Former | 12 (21.8%) | 98 (38.3%) | |
| Smoking duration, years | | | 0.34 |
| 26–30 | 11 (20.0%) | 37 (14.5%) | |
| 31–35 | 18 (32.7%) | 75 (29.3%) | |
| 36–40 | 14 (25.5%) | 90 (35.2%) | |
| 41–45 | 8 (14.5%) | 36 (14.1%) | |
| 46–50 | 1 (1.8%) | 13 (5.1%) | |
| >50 | 3 (5.5%) | 5 (2.0%) | |
| Time since quitting, years | | | 0.72 |
| <1 month | 0 (0.0%) | 1 (1.0%) | |
| 1–6 months | 0 (0.0%) | 8 (8.2%) | |
| 7 months–1 year | 1 (8.3%) | 10 (10.2%) | |
| 1–2 years | 0 (0.0%) | 12 (12.2%) | |
| 3–5 years | 4 (33.3%) | 34 (34.7%) | |
| 6–10 years | 7 (58.3%) | 33 (33.7%) | |
| Average daily cigarettes | | | 0.59 |
| 11–15 | 7 (12.7%) | 49 (19.1%) | |
| 16–20 | 11 (20.0%) | 66 (25.8%) | |
| 21–25 | 21 (38.2%) | 60 (21.4%) | |
| 26–30 | 8 (14.5%) | 70 (27.3%) | |
| 31–35 | 4 (7.3%) | 11 (4.3%) | |
| 36–40 | 2 (3.6%) | 17 (6.6%) | |
| 41–45 | 0 (0.0%) | 7 (2.7%) | |
| 46–50 | 0 (0.0%) | 2 (0.8%) | |
| 51–55 | 0 (0.0%) | 2 (0.8%) | |
| 56–60 | 1 (1.8%) | 3 (1.2%) | |
| >60 | 1 (1.8%) | 3 (1.2%) | |
| Education ^b | | | 0.02 |
| Primary/lower secondary [ISCED 1–2] | 28 (50.9%) | 133 (52.0%) | |
| Secondary [ISCED 3] | 15 (27.3%) | 59 (23.0%) | |
| Post secondary/non tertiary [ISCED 4] | 6 (10.9%) | 18 (7.0%) | |
| Tertiary (university level) [ISCED 5/6] | 4 (7.3%) | 46 (18.0%) | |
| Other/unknown | 2 (3.6%) | 0 (0.0%) | |
| Higher education | 6 (10.9%) | 44 (17.2%) | 0.31 |
| Chronic cough | 26 (47.3%) | 47 (18.4%) | <0.01 |
| Chronic sputum production | 20 (36.4%) | 37 (14.5%) | <0.01 |
| Dyspnea (at rest) | 5 (9.1%) | 7 (2.7%) | 0.01 |
| Avoiding physical efforts because of breathlessness | 7 (12.7%) | 15 (5.9%) | 0.07 |
| Persistent bronchial infections | 20 (36.4%) | 21 (8.2%) | <0.01 |
| Any of the above symptoms | 35 (63.6%) | 73 (28.5%) | <0.01 |

*, median (mean) values and IQR ranges [in square brackets] are reported for continuous variables, while n (%) are reported for categorical variables; ^b, German denomination of formal education level: Volks/Hauptschulabschluss [ISCED 1–2], Mittlere Reife [ISCED 3], Fachhochschule [ISCED 4], Hochschule [ISCED 5/6]. P values: for continuous variables these are derived using independent t-test, while for the categorical ones, the Fisher's exact test was used. FEV₁, forced expiration in one second; FVC, forced vital lung capacity; BMI, body mass index; ISCED, International Standard Classification of Education.

Table S4 Lung cancer cases who had COPD, classified by GOLD stage (GOLD-stage 1, GOLD 2, or GOLD stages 3–4), with comparison to cases who had normal spirometry

| Patient characteristics | COPD, GOLD 1 (n=92) | COPD, GOLD 2 (n=236) | COPD, GOLD 3–4 (n=41) | Normal spirometry (n=1,307) |
|---|------------------------|-------------------------|--------------------------|--------------------------------|
| Total detection/ diagnosed during screening period* | 0 | 15 | 4 | 33 |
| 1 st screening round* (“prevalence screening”) | 0 | 6 | 2 | 11 |
| 2 nd –5 th screening round* (“incidence screenings”) | 0 | 8 | 2 | 21 |
| Interval cases | 0 | 1 | 0 | 1 |
| Lung cancer cases diagnosed after the end of screening | 0 | 7 | 0 | 12 |
| Cumulative prevalence plus incidence, n (%) | 0 | 22 (9.3%) | 4 (9.8%) | 45 (3.4%) |
| P value | – | <0.01 | 0.06 | |
| Histology distribution, n (%) | | | | |
| Adenocarcinomas | 0 | 15 (68.1%) | 1 (25.0%) | 33 (73.3%) |
| Squamous-cell | 0 | 4 (18.2%) | 0 (0.0%) | 4 (8.9%) |
| Small-cell | 0 | 0 (0.0%) | 2 (50.0%) | 4 (8.9%) |
| Other | 0 | 3 (13.6%) | 1 (25.0%) | 4 (8.9%) |
| P value | – | 0.48 | 0.03 | |
| Stage distribution—screen-detected cases, n (%) | | | | |
| Stage 1 | 0 | 8 (36.4%) | 1 (25.0%) | 25 (55.6%) |
| Stage 2 | 0 | 6 (27.3%) | 1 (25.0%) | 5 (11.1%) |
| Stage 3 | 0 | 1 (4.5%) | 2 (50.0%) | 2 (4.4%) |
| Stage 4 | 0 | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 1 (2.2%) |
| P value | – | 0.03 | 0.04 | |
| Stage distribution—screen-detected plus further incident (all) cases, n (%) | | | | |
| Stage 1 | 0 | 11 (50.0%) | 1 (25.0%) | 27 (60.0%) |
| Stage 2 | 0 | 6 (27.3%) | 1 (25.0%) | 9 (20.0%) |
| Stage 3 | 0 | 2 (9.10%) | 2 (50.0%) | 4 (8.9%) |
| Stage 4 | 0 | 3 (13.6%) | 0 | 3 (6.7%) |
| Unknown | 0 | 0 | 0 | 2 (4.4%) |
| P value | – | 0.42 | 0.08 | |

*, P values are based on Fischer’s exact test.

Table S5 Median life expectancies and their 95% confidence intervals estimated from flexible parametric survival models for participants with spirometry patterns consistent with COPD, PRISm or absence of respiratory impairments (normal spirometry) (n=1,987)

| Life expectancy estimates (in years) n, (%) | PRISm (n=311, 15.7%) | COPD all GOLD stages (n=369, 18.6%) | Normal spirometry (n=1307, 65.8%) |
|---|----------------------|-------------------------------------|-----------------------------------|
| Overall | | | |
| Men (n=1,289, 64.9%) | 74.93 (73.28–76.94) | 75.71 (74.11–77.64) | 79.31 (77.45–81.78) |
| Women (n=698, 35.1%) | 80.36 (77.66–83.79) | 81.15 (78.36–84.73) | 84.80 (81.66–88.96) |

We obtained Life Expectancy estimates for the screening arm participants of the LUSI trial for which interpretable spirometry measurements were available (n=1,987). Our aim was to evaluate how the life expectancy estimates differ by spirometry patterns (categorical variable, 3 categories) consistent with COPD, PRISm or absence of respiratory impairments (normal spirometry), while simultaneously accounting for the following continuous baseline variables: age, BMI, average daily cigarettes, time since quitting smoking, and lifetime smoking duration. For this evaluation, we fitted flexible parametric survival models, assuming the Gompertz distribution for our data, and using the flexsurvreg function from the “flexsurv” package in R.