Increased Respiratory Morbidity in Individuals with Interstitial Lung Abnormalities

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Abstract

Background Interstitial lung abnormalities (ILA) are common in participants of lung cancer screening trials and broad population-based cohorts. They are associated with increased mortality, but less is known about disease specific morbidity and healthcare utilisation in individuals with ILA.

Methods We included all participants from the screening arm of the Danish Lung Cancer Screening Trial with available baseline CT scan data (n=1990) in this cohort study. The baseline scan was scored for the presence of ILA and patients were followed for up to 12 years. Data about all hospital admissions, primary healthcare visits and medicine prescriptions were collected from the Danish National Health Registries and used to determine the participants’ disease specific morbidity and healthcare utilisation using Cox proportional hazards models.

Results The 332 (16.7%) participants with ILA were more likely to be diagnosed with one of several respiratory diseases, including interstitial lung disease (HR: 4.9, 95% CI: 1.8-13.3, p=0.008), pneumonia (HR: 2.0, 95% CI: 1.4-2.7, p<0.001), lung cancer (HR: 2.7, 95% CI: 1.8-4.0, p<0.001) and respiratory failure (HR: 1.8, 95% CI: 1.1-3.0, p=0.03) compared with participants without ILA. These findings were confirmed by increased hospital admission rates with these diagnoses and more frequent prescriptions for inhalation medicine and antibiotics in participants with ILA.

Conclusions Individuals with ILA are more likely to receive a diagnosis and treatment for several respiratory diseases, including interstitial lung disease, pneumonia, lung cancer and respiratory failure during long term follow-up. The broadly increased respiratory morbidity can help explain the increased mortality in this population.
INTRODUCTION

Interstitial lung abnormalities (ILA) are a group of radiological findings visible on computed tomography (CT) of the lung in individuals without a diagnosis of interstitial lung disease (ILD).(1) They are common in participants of lung cancer screening trials, patients with chronic obstructive pulmonary disease (COPD) and broad population based cohorts. (2–8) These radiologic findings are also present in several interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis (IPF), and can precede onset of disease symptoms and diagnosis by several years. (1,9,10)

ILA are associated with increased mortality as well as reduced lung volumes and exercise capacity.(6,7,11) In addition, radiologic progression of ILA has been shown in longitudinal studies and it has been suggested that ILA represent subclinical ILD in some patients.(1,2,4,8,12) However, the prevalence of ILA is much higher than the prevalence of ILDs as clinical entities and only a few of all people with ILA develop clinical disease.(7,13–16) The role of ILA in the early detection of ILD remains to be established.

Several ILDs are known to lead to an increase in healthcare utilisation, including diagnostic procedures, hospital admissions, emergency department visits, medical treatment and lung transplantations.(17–19) However, data about the development of specific diseases and healthcare utilisation in individuals with ILA are still limited. The objective of this study was to investigate the association between incidental findings of ILA and disease specific morbidity such as the diagnosis of ILD and other diseases, hospital admission rates, primary care contacts and medicine use.

METHODS
Study population

All participants in the intervention arm of the Danish Lung Cancer Screening Trial (DLCST) with available CT scan data (n = 1990) were eligible for this registry-based follow-up cohort study. Methods of the DLCST, including criteria of eligibility, have been published previously and are briefly detailed below.(20) It was a 4-year, 5-round prospective randomized controlled screening trial. From 2004 to 2006, 4104 men and women aged 50–75 years with a smoking history of at least 20 pack-years were included in the study. Participants were recruited by newspaper ads. If participants were former smokers, they had to have quit after the age of 50 years and within the previous 10 years. Spirometry was performed by professionally trained and experienced hospital-based pulmonary function technicians or nurses, and were expressed in absolute values and as a percentage of predicted values according to European reference equations.(21) To be eligible for inclusion, FEV1 had to be at least 30% of the predicted value at baseline. Participants had to be able to climb two flights of stairs (total of 36 steps) without pausing. Exclusion criteria were weight over 130 kg, history of cancer diagnosis and treatment, lung tuberculosis, shortened life expectancy less than 10 years (according to the judgement of the recruiting physician), and chest CT performed during the past year for any reason.

Imaging and image review

Details about the imaging procedure have previously been published and are briefly described below.(20) The screening group was examined annually, using a multi-slice CT system (16 rows Philips Mx 8000, Philips Medical Systems). Scans were performed supine at full inspiration with a low-dose technique (120 kV and 40mAs). Visual assessment was performed on thin slices reconstructed with hard algorithm.
Two different sets of all scans in random order were created, and each set was evaluated by one of two observers (MMWW and LHT) who were blinded to person identification and date of scan. Interstitial lung abnormalities were registered as either absent or present, and if present further categorized as centrilobular, pleural, or paraseptal nodules, ground-glass attenuation, reticulation and/or honeycombing. The interobserver agreement in the detection of ILA was fair to substantial and has previously been published in more detail.\(^{(22)}\) Statistical analyses were performed on a combined ILA variable, classifying participants as having ILA if at least one observer noted a finding of ILA.

**Registries**

Registry data for all participants were obtained from the Danish national health registries covering the entire population. Data on public and private hospital admissions, outpatient clinic visits, emergency department visits and the diagnoses for these contacts were obtained from the Danish National Patient Register. Data on visits to a primary care provider were obtained from the Danish National Health Insurance Service Register. Data on medicine use were obtained from the Danish Prescription Database. Patients were followed up until May 5, 2016.

**Data analysis**

Analysis of baseline characteristics was performed with an unpaired t-test or Fisher’s exact test for continuous and categorical variables, respectively. Analysis of the association between ILA and the development of disease was based on all registered diagnoses (the primary discharge diagnosis and contributing or underlying diagnoses) for hospital admissions, outpatient clinic visits or emergency department visits. The ICD10-codes used to define the specific diseases and disease groups are listed in the supplementary material. We used Cox regression analysis to
handle the censoring that was introduced by the known increased mortality of participants with ILA.(13) Analysis of the association between ILA and hospital admission rates was exclusively based on the primary discharge diagnosis of hospital admissions to avoid overestimating chronic diseases that would often be listed as contributing diagnoses. Because of the possibility of repeated admissions with the same diagnosis, we used recurrent event Cox regression analysis using an Andersen-Gill model with death included as a censoring event. To adjust for within-subject correlation, the model included a count of previous admissions as a covariate. The multivariate Cox regression models were adjusted for age, sex, BMI and pack-years. An extended model which also included baseline measurements of FEV₁ was also used for the analysis of disease development. For the analyses of development of disease and hospital admission rates the proportional hazards assumptions of the Cox models were violated by pack-years and body mass index (BMI), which consequently were included as stratifying variables in the models, allowing for varying hazard functions. Cumulative event curves of expected hospital admissions are based on a marginal model of a recurrent event Cox proportional hazards model with gap times (patients were not at risk for admission while hospitalised), and a terminal event (death) model.(23) To control the false discovery rate that could result from multiple comparisons, we applied the Benjamini-Hochberg procedure to all p-values.

The associations between ILA and primary care visits or prescription medicine use were determined by negative binominal regression analysis, using observation time as offset to adjust for a shortened observation time caused by the increased mortality of participants with ILA.(13) The models were adjusted for age, sex, BMI.
and pack-years. The ATC codes used to classify prescription medicine are listed in the supplementary material.

Two-sided p-values below 0.05 were considered significant. Missing data were handled by listwise deletion without imputation of data. All statistical analyses were performed with the statistical software R (version 3.5.1).

RESULTS

The 332 (16.7%) participants of the Danish Lung Cancer Screening Trial with ILA were older, had lower FEV\textsubscript{1} % predicted and FVC % predicted, and had more frequently airway obstruction (FEV\textsubscript{1}/FVC < 0.7) at the time of their CT scan, compared with participants without ILA (Table 1).

| Table 1 | Baseline characteristics of participants with or without a baseline CT finding of ILA. |
|---------|----------------------------------------------------------------------------------|
| ILA (n = 332) | No ILA (n = 1658) | p-value |
| Age mean (SD), years | 59.7 (5.0) | 57.6 (4.7) | < 0.001 |
| Female, n (%) | 136 (41%) | 742 (45%) | 0.20 |
| BMI, mean (SD) | 24.9 (4.0) | 25.3 (3.8) | 0.06 |
| Current/former smokers, n (%) | 256/76 (77%/23%) | 1243/415 (74%/26%) | 0.41 |
| Pack-years, mean (SD) | 37.5 (13.4) | 36.18 (13.4) | 0.10 |
| FEV\textsubscript{1} l, mean (SD) | 2.75 (0.76) | 2.91 (0.75) | < 0.001 |
| FEV\textsubscript{1} % predicted, mean (SD) | 87.9 (18.6) | 92.4 (16.3) | < 0.001 |
| FVC l, mean (SD) | 4.03 (1.0) | 4.13 (0.99) | 0.10 |
| FVC % predicted, mean (SD) | 99.5 (17.7) | 101.7 (15.3) | 0.04 |
| FEV\textsubscript{1}/FVC < 0.7, n (%) | 178 (54%) | 693 (42%) | 0.001 |
| Follow-up time median, years (IQR) | 11.22 (10.77-11.75) | 11.29 (11.03-11.75) | < 0.001 |

ILA: interstitial lung abnormalities, SD: standard deviation, BMI: body mass index, FEV\textsubscript{1}: forced expiratory volume in one second, FVC: forced vital capacity

ILA and specific diagnoses

In multivariate Cox proportional hazards analysis, participants with ILA were more likely to be diagnosed with one of several respiratory, malignant or cardiovascular diseases, compared with those without ILA (Table 2, Fig. 1). Respiratory diseases
were most markedly increased, including COPD, pneumonia, pleural empyema or lung abscess, ILD and respiratory failure (Table 2). Moreover, we found an increase in gastrointestinal disease, which was driven by an increase in functional intestinal disorders (Table 2, Fig. 1). In an extended multivariate Cox proportional hazards model, also including the baseline measurement of FEV$_1$ as a covariate, COPD was no longer associated with ILA, while the other diagnoses remained unchanged (see supplementary material).
| Diagnosis                                   | ILA (%) | No ILA (%) | HR | 95% CI       | Adjusted p-value |
|--------------------------------------------|---------|------------|----|--------------|------------------|
| Respiratory                                | 116 (34.9) | 361 (21.8) | 1.6 | 1.3–2.0 | < 0.001 |
| COPD                                       | 55 (16.6)  | 159 (9.6)  | 1.7 | 1.2–2.3 | 0.01 |
| Pneumonia                                  | 56 (16.9)  | 126 (7.6)  | 2.0 | 1.4–2.7 | < 0.001 |
| Asthma                                     | 4 (1.2)    | 47 (2.8)   | 0.4 | 0.2-1.2  | 0.15 |
| Pleural empyema or lung abscess            | 5 (1.5)    | 3 (0.2)    | 6.6 | 1.5–28.8 | 0.03 |
| Interstitial lung disease                  | 8 (2.4)    | 8 (0.5)    | 4.9 | 1.8–13.3 | 0.008 |
| Respiratory failure                        | 25 (7.5)   | 61 (3.7)   | 1.8 | 1.1–3.0  | 0.03 |
| Malignant neoplasm                         | 93 (28.0)  | 317 (19.1) | 1.4 | 1.1–1.8  | 0.02 |
| Lung cancer                                | 39 (11.7)  | 71 (4.3)   | 2.7 | 1.8–4.0  | < 0.001 |
| Non-pulmonary cancer                       | 67 (20.2)  | 266 (16.0) | 1.2 | 0.9–1.6  | 0.30 |
| Cardiovascular                             | 157 (47.3) | 652 (39.3) | 1.2 | 1.0–1.5  | 0.09 |
| Heart failure                              | 19 (5.7)   | 47 (2.8)   | 1.7 | 1.0–3.0  | 0.19 |
| Pulmonary embolism                         | 8 (2.4)    | 22 (1.3)   | 1.9 | 0.8–4.3  | 0.17 |
| Atrial fibrillation/atrial flutter         | 27 (8.1)   | 95 (5.7)   | 1.3 | 0.8–2.0  | 0.34 |
| Ischemic heart disease                     | 50 (15.1)  | 174 (10.5) | 1.4 | 1.0–2.0  | 0.07 |
| Cerebral infarction                        | 18 (5.4)   | 59 (3.6)   | 1.4 | 0.8–2.3  | 0.34 |
| Peripheral vascular disease                | 21 (6.3)   | 50 (3.0)   | 2.0 | 1.2–3.4  | 0.04 |
| Gastrointestinal                           | 125 (37.7) | 489 (29.5) | 1.3 | 1.1–1.6  | 0.02 |
| GORD, gastritis or ulcer disease           | 25 (7.5)   | 95 (5.7)   | 1.3 | 0.8–2.1  | 0.30 |
| Functional intestinal disorders            | 28(8.4)     | 66(4.0)    | 2.2 | 1.4–3.4  | 0.006 |
| Musculoskeletal system and connective tissue | 140 (42.2) | 739 (44.6) | 1.0 | 0.8–1.2  | 0.89 |
| Inflammatory polyarthropathies             | 8 (2.4)    | 57 (3.4)   | 0.7 | 0.3–1.5  | 0.40 |

Number of participants with ILA compared with participants without ILA for receiving one of several specific diagnoses of interest at a hospital admission, outpatient clinic visits or emergency department visit. Cox regression analysis is adjusted for age, sex, BMI and pack-years. P-values are adjusted for multiple comparisons by the Benjamini-Hochberg method. ILA: interstitial lung abnormalities, HR: hazard ratio, COPD: chronic obstructive pulmonary disease, GORD: gastro-oesophageal reflux disease.

ILA and hospital admission rates

Participants with ILA had a higher crude mean admission rate during follow-up compared with participants without ILA (39 vs. 23 admissions per 100 person-years at risk) (Fig. 2). In a multivariate recurrent event Cox proportional hazards analysis,
participants with ILA had a significantly higher hazard rate for hospital admission during short-term (1 year) follow-up (HR: 1.8, 95% CI: 1.3–2.6, p = 0.002) and long-term (12 years) follow-up (HR: 1.4, 95% CI: 1.2–1.7, p < 0.001) (Fig. 3). After stratifying hospital admissions by discharge diagnoses, we found a significant increase in admissions due to respiratory and malignant diseases in participants with ILA (Table 3, Figs. 2 and 3). Most notably, admissions for pneumonia and lung cancer were more frequent (Table 2). Hospital admissions for COPD were not associated with ILA when only considering the primary discharge diagnosis (Table 3). However, when expanding the analysis to include all discharge diagnoses (primary diagnosis and contributing diagnoses), participants with ILA had more frequent hospital admissions also with COPD (HR: 2.1, 95% CI: 1.3–3.3, p = 0.003). Hospital admissions with cardiovascular disease were increased in the unadjusted model (Fig. 3) but not in the multivariate model (Table 3). However, admission for pulmonary embolism and peripheral vascular disease were consistently increased in participants with ILA (Table 3). The hazard rate of emergency department visits was similar in participants with or without ILA (HR: 1.3, 95% CI: 0.8–2.0, p = 0.36).
Table 3

Disease specific hospital admissions and emergency-department (ED) visits in participants with or without ILA.

| Disease group                              | HR   | 95% CI  | Adjusted p-value |
|--------------------------------------------|------|---------|-----------------|
| Respiratory disease                        | 2.1  | 1.4–3.1 | 0.001           |
| COPD                                       | 2.5  | 0.9–6.8 | 0.10            |
| Pneumonia                                  | 2.1  | 1.5–3.0 | 0.001           |
| Asthma                                     | 0.8  | 0.1–7.7 | 0.90            |
| Pleural empyema or lung abscess            | 0.3  | 0.0–32.6| 0.90            |
| Interstitial lung disease                  | 1.8  | 0.3–12.5| 0.82            |
| Malignant neoplasm                         | 1.6  | 1.2–2.1 | 0.001           |
| Lung cancer                                | 2.8  | 1.7–4.5 | 0.001           |
| Non-pulmonary cancer                       | 1.3  | 0.9–1.9 | 0.15            |
| Cardiovascular disease                     | 1.4  | 1.0–1.8 | 0.10            |
| Heart failure                              | 2.2  | 1.3–4.1 | 0.09            |
| Pulmonary embolism                         | 4.9  | 1.6–14.7| 0.01            |
| Atrial fibrillation/atrial flutter         | 1.3  | 0.5–3.3 | 0.82            |
| Ischemic heart disease                     | 1.1  | 0.8–1.6 | 0.90            |
| Cerebral infarction                        | 1.5  | 0.8–2.7 | 0.43            |
| Peripheral vascular disease                | 5.0  | 2.5–9.9 | 0.001           |
| Gastrointestinal disease                   | 1.1  | 0.8–1.6 | 0.87            |
| GORD, gastritis or ulcer disease           | 0.9  | 0.3–2.2 | 0.90            |
| Functional intestinal disorders            | 1.1  | 0.4–3.0 | 0.90            |
| Diseases of the musculoskeletal system and connective tissue | 1.1  | 0.8–1.4 | 0.90            |
| Inflammatory polyarthropathies             | 1.5  | 0.9–2.4 | 0.95            |

Adjusted hazard ratios for disease specific hospital admissions and emergency-department (ED) visits in participants with ILA compared with participants without ILA. Cox regression analysis is adjusted for age, sex, BMI and pack-years. P-values are corrected multiple comparisons by the Benjamini-Hochberg method. ILA: interstitial lung abnormalities, HR: hazard ratio, GORD: gastro-oesophageal reflux disease

ILA and primary care visits

The rate of visits to a primary care provider during follow-up was slightly increased in participants with ILA compared with participants without ILA (4.51 vs. 4.05 visits per person year at risk, \( p = 0.01 \)). However, this difference was no longer significant in the multivariate model (see supplementary material).

ILA and medicine use

Participants with ILA had a higher overall rate of collected drug prescriptions during follow-up (median 3.1 vs. 2.5 prescriptions per person year at risk, \( p = 0.009 \)). After adjusting for potential confounders in multivariate negative binomial regression
analysis, there remained an increased use of several medications, including inhalation therapy \((p = 0.009)\), antibiotic therapy \((p = 0.002)\) and loop diuretics \((p = 0.008)\) (Table 4).

**Table 4**

| Medication                        | ILA  | No ILA | p-value |
|-----------------------------------|------|--------|---------|
| Inhalation therapy                | 72 (22%) | 316 (19%) | 0.009   |
| Antibiotic therapy                | 277 (83%) | 1337 (81%) | 0.002   |
| Prednisolone                      | 27 (8%) | 130 (8%) | 0.63    |
| Proton pump inhibitors            | 111 (33%) | 482 (29%) | 0.07    |
| Antithrombotic therapy            | 98 (30%) | 361 (22%) | 0.35    |
| Antihypertensive therapy          | 77 (23%) | 348 (21%) | 0.09    |
| Loop diuretics                    | 27 (8%) | 79 (5%) | 0.008   |
| Lipid lowering therapy            | 108 (33%) | 517 (31%) | 0.64    |
| Antidiabetic therapy              | 75 (23%) | 335 (20%) | 0.86    |

P-values based on negative binomial regression of the number of prescriptions, adjusted for age, sex, BMI and pack-years. ILA: interstitial lung abnormalities

**DISCUSSION**

In this 12-year long follow-up study of the Danish Lung Cancer Screening Trial population we show an increased disease specific morbidity and healthcare utilisation in participants with ILA. This includes a more frequent diagnosis of several respiratory diseases, such as ILD, pulmonary infections, lung cancer and respiratory failure, a higher hospital admission rate, and higher use of several therapies for these diseases.

**ILA and specific diagnoses**

A higher proportion of participants with ILA received a hospital diagnosis of a respiratory disease or lung cancer in the 12 years following the radiologic finding. Our results add to previous reports of increased lung cancer related mortality and to a lesser extent respiratory mortality in individuals with ILA. (7,13,24) However, the present study adds to the understanding of ILA by describing an increased frequency of several more specific respiratory diagnoses, such as ILD, pneumonia, pleural empyema and respiratory failure, after adjusting for age, sex, BMI and
smoking status. It is not clear how the presence of ILA predisposes to the increased morbidity, but these rather unspecific radiological findings possibly reflect inflammatory, premalignant or pulmonary vascular changes. ILA could also be the result of previous exposure to dust, gasses, infections or pneumotoxic medications, in a population already predisposed to respiratory diseases.

The association between ILA and the development of clinical ILD highlights the potential for an earlier diagnosis by recognizing ILA in a lung cancer screening setting. (25) It adds to previous findings of increased incidence of ILD in individuals with areas of increased lung attenuation. (24) In IPF, radiological findings can be visible many years before clinical disease, making screening by CT in conjunction with lung cancer screening an attractive option. (10, 25) Considering that IPF is more common in smokers and older people, who also are the candidate population for lung cancer screening, it is possible that some cases of subclinical IPF could be detected as incidental findings from the CT scans in a lung cancer screening program. (25, 26)

The marked increase in pulmonary infections in participants with ILA was confirmed by an increased use of antibiotics. This association could have several explanations. Firstly, patients with ILA were older and more frequently active smokers, and thus more susceptible to pneumonia. (27) Secondly, the higher frequency of COPD, a disease associated with pulmonary infections and exacerbations, in participants with ILA would lead to an expected increase in these infections.

In line with the general increase in respiratory disease, a hospital diagnosis of respiratory failure was twice as frequent in participants with ILA compared with those without ILA. A previous study has shown that critically ill patients with sepsis, who had ILA on chest CT scans taken within one week prior to ICU admission were
more likely to develop acute respiratory distress syndrome. (28) We supplement these findings with longitudinal follow-up showing that a finding of ILA also increases the long-term risk of developing respiratory failure.

ILA and hospital admission rates

Participants with ILA had a higher rate of hospital admissions during both short-term and long-term follow-up. Hospital admission rates are measures of morbidity that are highly relevant to both patients and healthcare systems, and are a recommended outcome for clinical trials of IPF alongside mortality. (29,30) Our results thus highlight the clinical and economical importance of ILA as incidental findings. (13)

The most pronounced increase in hospital admissions for participants with ILA was found for respiratory and malignant causes, which corresponds with our finding of an increased incidence of these diseases in participants with ILA. The increased rate of hospital admissions with pulmonary embolism and peripheral vascular disease in participants with ILA was more surprising. Venous thromboembolic disease is associated with several ILDs, including lung fibrosis, sarcoidosis and IPF. (31–34) To our knowledge, we present for the first time an increase in pulmonary embolism morbidity also in individuals with ILA. The higher prevalence of malignancy, which is a known risk factor for thromboembolic disease, in participants with ILA could be a possible explanation. Alternatively, ILA and thromboembolic disease could share common, and possibly unknown, risk factors.

Limitations

There is a lack of standardization of ILA across different studies which makes comparisons difficult. (35) In contrast to other reports, we did not code any findings as ‘indeterminate’ or ‘equivocal’ but limited the analysis to a dichotomous variable
of ‘ILA’ or ‘No ILA’. This potentially weakened our conclusions by including less severe findings in the ‘exposed’ group. However, any cut-offs between different grades of severity would be arbitrary and not easily transferred to clinical practice, which could make them difficult to interpret. In addition, we relied on qualitative descriptors of ILA rather than quantitative measures. This reduces the repeatability of our findings due to the known interobserver variability of radiologic findings even among experienced radiologists. (36) However, our approach is similar to the use of imaging in clinical practice and research. (2,4,7)

The data on the specific contact diagnoses were only available for secondary care contacts (hospital admissions, outpatient clinic visits and emergency department visits). This could lead to potentially underestimating the prevalence of a certain diagnosis (i.e. COPD or pneumonia) for participants treated exclusively in primary care. However, for many diagnoses of interest, such as lung cancer and ILD, participants would be expected to be diagnosed in secondary care.

Conclusions

Individuals with ILA have an increased morbidity related to several respiratory diseases, including ILD, pulmonary infections, lung cancer and respiratory failure. These findings can help to explain the increased mortality in this population and should be taken into account in their healthcare plans.

Abbreviations

ILA
interstitial lung abnormalities
ILD
interstitial lung disease
IPF
idiopathic pulmonary fibrosis
CT
computed tomography
COPD
chronic obstructive pulmonary disease
DLCST
Danish lung cancer screening trial
BMI
body mass index
FEV₁
forced expiratory volume in one second
FVC
forced vital capacity

Declarations

Ethics approval and consent to participate
The DLCST was approved by the Ethics Committee of Copenhagen County. Approval of data management in the trial was obtained from the Danish Data Protection Agency. All participants provided written informed consent and the study was conducted according to the principles of the Declaration of Helsinki. This follow-up study was approved by the Danish Data Protection Agency (HGH-2016-017).

Consent for publication
Not applicable.

Availability of data and materials
The datasets used and/or analysed during the current study are available in an anonymized form from the corresponding author on reasonable request.

Competing interests
Dr. Hoyer reports grants from Roche a/s, grants from Skibsreder Per Henriksen, R. og Hustrus Fond, grants from P.A. Messerschmidt og Hustrus Fond outside the submitted work. Dr. Hohwü Thomsen has nothing to disclose. Dr. Winkler Wille has nothing to disclose. Dr. Wilcke has nothing to disclose. Dr. Dirksen has nothing to disclose. Dr. Holst Pedersen has nothing to disclose. Dr. Ashraf has nothing to disclose. Dr. Saghir has nothing to disclose. Dr. Shaker reports personal fees from Roche and personal fees from Boehringer Ingelheim, outside the submitted work.

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**Authors' contributions**

NH, TW and SS conceived the idea of this follow-up study. LHT and MMWW read the CT scans. AD, JHP, HA, ZS, LHT and MMWW performed the original screening study. NH collected and analysed the registry data. NH created the first draft of the manuscript. All authors read and approved the final manuscript.

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**Authors' information (optional)**

Not applicable.

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Figures
Figure 1

Hazard ratio for participants with ILA compared with those without ILA for developing a disease within a year of exposure analysis is adjusted for age, sex, BMI and pack-years. Error bars represent 95% confidence intervals.
Figure 2

Unadjusted hospital admission rates in participants with ILA and those without ILA.
Figure 3

Expected number of hospital admissions in participants with ILA and without ILA

Supplementary Files

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