



## Interstitial lung abnormalities and physical function

To the Editor:

The term interstitial lung abnormalities (ILA) was coined to define a precursory stage of idiopathic pulmonary fibrosis and encompasses a set of radiological changes seen in interstitial lung diseases (ILD) but are often of lesser magnitude [1]. ILA have been associated with age, many environmental and genetic risk factors and pulmonary symptoms of idiopathic pulmonary fibrosis [1, 2]. ILA have also been associated with reduced exercise capacity and self-reported health and function [3–5].

Given that ILA are associated with ageing and reduced exercise capacity, the goal of this study was to determine if more diverse markers of physical function were associated with ILA. We proposed five markers of physical function: hand grip strength, knee extension strength, gait speed, the timed up and go test, and thigh muscle mass. These markers are recognised measures of physical function in the elderly [6]. These measures have been associated with mortality [7–9] as well as various markers of disability or poor health outcomes [10, 11].

Data from the Icelandic Heart Association's Age, Gene/Environment Susceptibility-Reykjavik Study (AGES-Reykjavik Study) were used. Details of the study design have been previously described [12].

Informed consent was obtained from all participants. The AGES-Reykjavik Study was approved by the National Bioethics Committee in Iceland (VSN: 00-063) and by the National Institute on Aging Intramural institutional Review board [12].

ILA status was determined by jointly evaluating two thoracic computed tomography scans per participant. Each evaluation was carried out by up to three specialised readers; details of this methodology and the definition of ILA have been previously published [13]. Participants were also categorised into one of four subtypes of ILA [1]. The four subtypes were: predominantly centrilobular or peribronchial abnormalities; predominantly subpleural abnormalities; mixed centrilobular and subpleural abnormalities; and radiographic evidence of ILD.

Muscle mass was assessed by quantifying total muscle area in  $\text{cm}^2$  with computed tomographic imaging, as previously described [9]. The odds ratios provided are per a decrease of  $10 \text{ cm}^2$ . Isometric knee extension strength was measured using an adjustable dynamometer chair as previously described [14]. Hand grip strength of the dominant hand was measured by a computerised dynamometer as previously described [15]. The odds ratios for grip strength and knee extension strength are based on a decrease of 100 Newtons (N). Gait speed was quantified by measuring seconds required to walk a 6-m long course [14]. The tasks included in the timed up and go test were standing up from an arm chair, walking 3 m, walking back to the chair and sitting down again.

Participants with indeterminate ILA status were excluded from statistical analyses ( $n=1726$ ), as were participants for which thoracic computed tomography scans were not available ( $n=444$ ).

Logistic regression modelling was employed for analysis of explanatory variables' association with ILA. Two models were constructed (table 1). One is a univariate model of the association of the explanatory variables with ILA while the other is a multivariable model of the same association in which sex, body mass index (BMI), age, pack-years of smoking and current smoking status were included as covariates.



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**Reductions in objectively measured physical function are associated with interstitial lung abnormalities** <http://ow.ly/azAW30kMhqv>

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TABLE 1 Associations of functional markers with ILA status and subtypes of ILA

	Subjects n (%)	Decreased grip strength (100 N)	Decreased knee extension strength (100 N)	Timed up and go test (s)	Gait speed during 6 m walk (s)	Decreased thigh muscle mass (10 cm <sup>2</sup> )
<b>Unadjusted model</b>						
ILA status	378	1.00 [0.90–1.11]; 0.99	1.04 [0.94–1.14]; 0.45	1.06 [1.03–1.10]; 0.0001	1.09 [1.04–1.14]; 0.0002	1.00 [0.96–1.05]; 0.85
<b>Adjusted model</b>						
ILA status	378	1.21 [1.02–1.42]; 0.024	1.23 [1.07–1.41]; 0.0036	1.03 [1.00–1.07]; 0.065	1.06 [1.01–1.12]; 0.026	1.14 [1.05–1.23]; 0.0008
<b>ILA subtypes</b>						
Centrilobular abnormalities	40 (10.6)	0.97 [0.60–1.58]; 0.91	1.05 [0.72–1.54]; 0.79	0.96 [0.81–1.13]; 0.64	0.94 [0.75–1.19]; 0.63	0.99 [0.77–1.25]; 0.90
Subpleural abnormalities	236 (62.4)	1.24 [1.02–1.52]; 0.034	1.28 [1.08–1.52]; 0.0039	1.03 [0.99–1.07]; 0.18	1.03 [0.96–1.10]; 0.42	1.17 [1.07–1.28]; 0.0006
Mixed abnormalities	85 (22.5)	1.23 [0.89–1.71]; 0.21	1.27 [0.96–1.68]; 0.097	1.04 [0.97–1.12]; 0.24	1.12 [1.03–1.21]; 0.0071	1.09 [0.93–1.28]; 0.26
Radiographic ILD	17 (4.5)	1.20 [0.61–2.34]; 0.59	0.93 [0.52–1.65]; 0.80	1.10 [0.98–1.22]; 0.11	1.16 [1.02–1.32]; 0.020	1.09 [0.78–1.52]; 0.62

Data are presented as OR (95% CI); p-value, unless otherwise stated. Associations were estimated with logistic regression models. Odds ratios represent the change in interstitial lung abnormalities (ILA) risk per unit change of the variable in question. For example, a 100 N decrease in grip strength is associated with a change in ILA odds by a factor of 1.21 in the adjusted model. Unadjusted model: a univariate model of the association of ILA status to the explanatory variable; adjusted model: a multivariate model adjusted for sex, body mass index (BMI), age, pack-years and current smoking status as covariates; ILA subtypes: A multivariate model adjusted for sex, BMI, age, pack-years and current smoking status as covariates. In analyses of each ILA subtype, participants with other subtypes are excluded so the results, given as odds ratios represent the change in the odds of the specified subtype. ILD: interstitial lung disease.

Associations with ILA subtypes were also explored (table 1), using the same multivariable logistic models as the general ILA analyses. In modelling of each ILA subtype, participants with other ILA subtypes were excluded. All statistical analyses were done using R.

The results of logistic regression models exploring the associations of functional markers with ILA are displayed in table 1. As shown in table 1, decreased performance in four out of five markers of physical function was significantly associated with an increased risk of ILA in models adjusted for relevant covariates. These markers were decreased grip strength, decreased knee extension strength, decreased thigh muscle mass and an increase in time required to walk 6 m.

The 378 study participants with ILA were classified into subtypes of ILA as follows: 40 participants (10.6% of participants with ILA) were determined to have the centrilobular subtype, 236 (62.4%) had subpleural abnormalities, 85 (22.5%) had mixed abnormalities and 17 (4.5%) had the radiographic interstitial lung disease subtype (table 1).

As shown in table 1, decreased grip strength, knee extension strength and thigh muscle mass were associated with increased risk of the subpleural abnormalities subtype of ILA. Gait speed was inversely associated with the risk of the mixed abnormalities subtype and the radiographic ILD subtype. No markers were significantly associated with the centrilobular subtype of ILA and performance in the timed up and go test did not have significant associations with any of the markers measured.

In this study, we explored the associations of a broader spectrum of physical capabilities with interstitial lung abnormalities than previously reported, demonstrating that decrements in several measures of physical function are associated with increased risk of interstitial lung abnormalities. The associations were found to differ between known subtypes of ILA. These findings support previous studies reporting that ILA are associated with reduced measures of exercise capacity [3, 4] and extend these findings by demonstrating that a broader spectrum of objective physical function measures is associated with ILA.

Although the reasons for the associations presented here are not entirely clear, there are several conceivable explanations for these findings. One plausible possibility is that ILA and declining physical function, at least in some cases, may be driven by similar biological processes, such as age-related processes. A second possibility is that relative reductions in lung capacity [1] and gas exchange [2] could lead to reductions in exercise capacity and strength overall.

In previous analyses of subtypes of ILA, the subtype associated with the greatest physiological effect was the radiographic ILD subtype while the subpleural abnormalities and mixed abnormalities subtypes were associated with a lesser effect [1, 3]. Centrilobular predominant ILA is reported to have minimal or no physiological effect [1, 3]. Our findings are consistent with this prior work, apart from the limited associations of ILA with radiographic ILD. This may be explained by a lack of power to detect these associations, as only 17 individuals had this subtype in the AGES-Reykjavik cohort.

This study has several limitations. The cross-sectional nature of the study makes it impossible to presume causal mechanisms. Although this study demonstrates that those with ILA have reduced measures of physical function by multiple measurements, the biological mechanisms leading to this finding are not known. Additionally, replication of these findings will be important, in part due to the possible existence of unknown confounders or confounders not adjusted for, such as pulmonary function and other comorbidities, and to better define the role of important confounders, such as age, in the findings.

These results support the conclusion that ILA either occurs in people that have worse physical condition than people without ILA, or that ILA results in reduced measures of physical function. Both these suggestions are interesting, especially when viewed in the context of previous reports of people with ILA having an increased risk of mortality [13] and worse subjectively assessed health [5]. Future longitudinal studies exploring the timing of these associations would be of interest.

In conclusion, markers of decreased physical function were found to be associated to interstitial lung abnormalities. These associations differed among subtypes of ILA. The findings suggest that ILA's effect on physical capabilities is greater than previously described and have implications for further research.

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