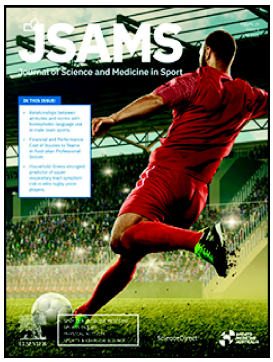

Physical activity, exercise capacity and mortality risk in people with interstitial lung disease: a systematic review and meta-analysis

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Physical activity, exercise capacity and mortality risk in people with interstitial lung disease: a systematic review and meta-analysis

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Abstract

Objectives: Physical activity (PA) and exercise measures show potential to predict mortality in people with interstitial lung disease (ILD). This study summarized evidence on the association between PA and exercise capacity measures and mortality risk in people with ILD and quantified its magnitude by meta-analysis.

Methods: PubMed, Scopus, Web of Science and EBSCO were searched until May 2020 with updates until September 2021. Two authors screened studies, extracted data, and assessed risk of bias. A random-effects meta-analysis for each PA measure was conducted using logarithmic hazard ratios.

Results: Fifty-two studies of 10349-people with ILD (64±9years;67%men) were included. A significant association between at least one measure of PA and exercise and mortality risk was found in 44-studies. Most reported measures were six-minute walk test (6MWT), oxygen uptake (VO_2), work (watts-W) and time spent in PA. Meta-analysis showed that individuals with 6MWD<250meters had more than twofold higher mortality risk, than those with 6MWD≥350meters. Individuals presenting a 6MWD decrease≥26meters over 6-48months showed an almost threefold higher mortality risk. An increase of 10-20W or 10%predicted in workload and a time spent in PA≥100minutes/week or ≥0.031kcal/min/kg/day were associated with an overall 12% and 45% lower mortality risk, respectively.

Conclusions: PA and exercise capacity measures were associated with mortality risk in people with ILD. Most studies used the 6MWT and more evidence is needed on the other measures (i.e., VO_2, work and PA time). Personalized interventions to improve PA and exercise capacity should be considered to delay premature mortality in people with ILD.

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Graphical abstract

Keywords: Respiratory Tract Diseases; Physical activity; Exercise capacity; Review literature; Survival.

1. Introduction

Interstitial lung disease (ILD) is a highly disabling group of chronic respiratory diseases characterized by different degrees of lung inflammation and fibrosis [1]. The most common ILD conditions are idiopathic pulmonary fibrosis (IPF), acute and chronic interstitial pneumonias, connective tissue diseases and sarcoidosis which are associated with high levels of premature mortality [1]. ILD is an independent risk factor for all-cause mortality[2] and is related to a 5-year mortality rate varying from 8.4% to 64.6% in its different subtypes [2].

Screening individuals with the highest mortality risk at the time of diagnosis along with an accurate prognosis is important to improve clinical meaningful decision making [3]. However, this has been truly challenging since individuals show a high heterogeneous disease course of progressive morbidity and early death [1]. Moreover, evidence is not yet consistent on the best clinical measures to predict disease progression and mortality risk [4] to be used in clinical practice [4].

Lung function indices are currently the most used predictors of mortality at the time of diagnosis [3,5,6]. Nevertheless, physical activity (PA) and exercise capacity measures also show potential as predictors of mortality in people with ILD since individuals often present several pathophysiological mechanisms that limit their ability to perform PA and exercise such as, gas exchange and pulmonary circulation impairment, ventilatory restriction and muscle dysfunction [7]. There are prior studies showing that reduced PA measured by time spent in PA per day [8], lower exercise capacity with six-minute walk test (6MWT) [3,6,9] or decreased peak oxygen uptake (VO_2 peak) [10,11] is associated with a higher mortality risk in people with ILD, however summary estimates on the magnitude of these associations are scarce and only include people with IPF [12,13]. Evidence suggests that the 6MWT might be a good indicator of mortality risk, due to its clinically significance, ability to assess aerobic capacity and association with pulmonary and extrapulmonary manifestations of the disease [3,6]. In fact, the VO_2 peak achieved during a 6MWT has shown to be equivalent to the one obtained during cardiopulmonary exercise test (CPET), a gold standard to assess exercise capacity, in people with ILD [10,11]. Moreover, the 6MWT is easy to implement, requires minimal resources and equipment, and

can be performed across different health care settings, leading to a high level of acceptance by patients and health professionals[3,8].

There are however other PA and exercise capacity measures used for clinical decision-making, setting prognosis and assessment of disease progression is not widely implemented among health professionals, despite its simple, safe and non-invasive application, and their routine use for assessing people with respiratory diseases [14]. Thus, evidence on the magnitude of association between the different PA and exercise capacity measures and mortality risk is required to support the use of these measures for clinical decision-making, setting prognosis and assessing mortality risk.

This systematic review aimed to summarize evidence on the association between PA and exercise capacity measures and mortality risk in people with ILD; and to quantify its magnitude by conducting a meta-analysis.

2. Methods

2.1 Literature search

Searches in the PubMed and the International Prospective Register of Systematic Reviews (PROSPERO) were conducted prior to the development of the present systematic review to exclude the existence of reviews or protocols with the same purpose of this one. No similar studies were found, and the review protocol was registered and is available at PROSPERO (registration no. CRD42020187952).

This systematic review including meta-analysis was performed in accordance with Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA, 2021). A systematic literature search was performed by a researcher on the 27th of May 2020 on the following electronic databases: PubMed, Scopus, Web of Science and EBSCO. Weekly automatic updates from each database were weekly checked until September 2021. Search terms were based on a combination of keywords including all types of PA, exercise, mortality-related words and ILD terms also including its subtypes. The following PA definition was used for the purpose of this systematic review "any body movement produced by the contraction of skeletal muscles that causes substantial energy expenditure beyond resting values and includes physical fitness (i.e., a set of measurable health-related or skill-related attributes or characteristics individuals have or achieve that are related to their ability to perform PA) and exercise (i.e., planned, structured and repetitive PA performed to improve or maintain one or more components of physical fitness)" [15].

Full search expression for each database is available in Text S1 (supplementary material). The search had no predefined filters and was limited to terms found in titles, abstracts, and keywords. Reference lists of the selected articles were also scanned for other potential eligible studies. Authors were contacted to obtain full texts when needed.

2.2 Eligibility criteria and study selection

Studies were considered eligible if they: i) included adults (≥18 years of age) with ILD; ii) were written in English, Portuguese, French, Italian or Spanish; iii) were experimental or observational studies; and iv) described at least one measure of association between PA and exercise measures and survival in people with ILD. Review articles, qualitative studies, magazines, news, research protocols, thesis, reports, dissertations, abstracts, communications, posters, letters to the editor, unpublished work, editorials, commentaries, books, book chapters without original data, guidelines, statements, position papers and case studies were excluded.

After removing duplicates, two reviewers independently screened all titles, abstracts and keywords and retrieved potentially eligible articles for full text review using EndNote X9 (Version 9.3, Porto, Portugal). Disagreements were discussed and resolved by consensus with a third researcher (AM).

2.3 Data extraction and quality assessment

Data extraction retrieved information on: authors, year, country, study design, study population, PA and exercise measures, observation period, statistical method used to investigate the relationship between these measures and mortality, estimates of effect and the respective 95% confidence intervals (95%CI) for univariate and multivariate models, the variables included in the multivariate model and a summary of key findings.

The risk of bias in each study was assessed independently by two researchers (VR and VN) using the Newcastle–Ottawa Scale (NOS) [16], one of the most recommended scales for evaluating cohort studies. The original eight-item NOS for cohort studies was used to assess the three key areas of potential bias: selection of participants, comparability and measurements. The score ranges between zero and nine stars, with more stars being associated with a lower risk of bias. More details on the items assessed can be found in supplementary table S1. Additionally, the inter-rater agreement of the quality assessment performed by the two reviewers was evaluated using Cohen's

kappa. The value of Cohen's kappa ranges from zero to one, illustrating a slight (≤0.2), fair (0.21–0.4), moderate (0.41–0.6), substantial (0.61–0.8), or almost perfect (≥0.81) agreement.

2.4 Data analysis

The primary outcome was overall mortality. Studies were grouped according to the type of PA and exercise measure reported. Only studies reporting hazard ratios (HR) for the most reported measures were included in the meta-analysis. The HR were interpreted as: an HR=1 represents lack of association between the exposure (PA and exercise capacity) and the outcome (mortality risk); an HR greater than 1 suggests an increased risk; and an HT below 1 suggests a reduced risk. Forest plots were computed using univariate estimates to allow comparison across studies, since in multivariate analysis different factors were considered in each study. Studies were represented once per meta-analysis except when different PA and exercise measures were available for the same study. Studies-specific estimates were combined using inverse variance-weighted averages of logarithmic HR assuming a random-effects model, to account for both within-study and between-study variances. Between-study heterogeneity was quantified using I-squared (I^2) statistic. This statistic describes the percentage of variation across studies due to heterogeneity rather than chance, and values of 0-24%, 25-75%, and ≥75% indicate low, moderate, and high levels of heterogeneity, respectively. For each measure of PA, publication bias was assessed qualitatively through visual inspection of funnel plots and quantitatively using the Begg rank correlation test and Egger regression test for funnel plot asymmetry. A broadly symmetrical plot indicates a lower risk of bias against the publication of negative results.

Subgroup analyses were performed: 1) by presenting the HR only for people with IPF in the 6MWT meta-analysis, since this is the most common ILD subtype; 2) by applying a fixed-effects model assuming an equal effect size across studies; 3) and by investigating the influence of each individual study on the overall meta-analysis estimate. All analyses were carried out with STATA (V.15.0, StataCorp, College Station, Texas, USA).

3. Results

3.1 Study selection and risk of bias across studies

Figure 1 presents the literature search flow diagram. The systematic database search identified 4852 publications. After removing duplicates, title, abstract and keywords were screened for 3124 papers. From these, 213 papers were full text screened. The weekly automatic updates suggested 239 studies and after screening six additional studies were retrieved. A total of 52 observational studies were included. Results of the quality assessment showed that five papers[10,17-20] (10%) scored as low quality, presenting less stars that the median (4.5) of the total score (supplementary table S1). The agreement between the two reviewers was substantial (k=0.62, 95%CI 0.46-0.78, p<0.001) and a final consensus was reached.

3.2 Study characteristics

The characteristics of the 52 included studies are shown in table S2 (supplementary material). Studies were published between 2001 [21] and 2021 [22] and most were conducted in the United States of America [9,18,19,21,23-32], Japan [8,33-39] and Israel [11,40-44]. Included studies comprised data from 10349 people with ILD: 8071 people with IPF, 1365 with non-specified ILD, 359 with connective-tissue disease-ILD (CTD-ILD), and the remaining cases included people with other ILD subtypes. Participants mean age was 64±9 years, 67% were men and presented a mean diffusing capacity for carbon monoxide (DL_{CO}) of 48.3±15.7 %predicted and a mean forced vital capacity (FVC) of 68.2±17.4%predicted. The studies' observation period ranged from 23 days to 15.5 years (detailed information can be found in Table S2, supplementary material).

3.3 Physical activity measures and all-cause mortality

From the 52 included studies, 44 reported a significant association between at least one measure of PA and exercise capacity with mortality risk, showing that an increase in PA or exercise capacity was associated with lower mortality risk or that a decrease in PA or exercise capacity was associated with higher mortality risk. Most reported measures were the six-minute walk distance (6MWD) (n=42),

the VO_2 peak or VO_2 max (n=10), the work in watts (n=5) and the time spent in PA measured with accelerometry and questionnaires (n=4).

From the 42 studies using the 6MWT, 35 [3,6,8-10,17-19,22,26,28,29,31,33,34,36-38,40,41,43,45-58] showed a significant association between the distance walked and mortality risk.

Results of the 6MWT meta-analysis showed that in participants walking more than 350m, an increase of 50m over time was associated with a 20% lower mortality risk (Figure 2). A twofold higher mortality risk was found among participants walking between 250m and 350m [subtotal HR: 2.10 95%CI (1.49; 2.95)] and on those walking less than 250m [HR: 2.49, 95%CI (1.67;3.70)], compared to people with ILD with a 6MWT≥ 300m or 350m with no evidence of heterogeneity (Figure 2). In addition, a decrease ≥26m in 6MWD over time (6-48 months) was associated with about threefold higher mortality risk [subtotal HR: 2.57 95%CI (1.90;4.58)], nevertheless high heterogeneity (I^2=78.9%; p<0.001) was found (Figure 2).

VO_2 max and VO_2 peak overall estimates were associated with a 10% lower mortality risk (Figure 3).

Overall, an increase in work (W) was associated with a 12% lower mortality risk (Figure 4). Specifically, an increase of 10% in predicted workload was associated with 8% lower mortality risk and an increase in percentage of work was associated with a 4% lower mortality risk (I^2=67.5%; p=0.046).

Time spent in PA≥0.03 1kcal/min/kg per day or ≥100minutes per week, measured with accelerometry and in-person questionnaires, was significantly associated with 45% lower mortality risk, with high heterogeneity (I^2=79.3%; p<0.001) (Figure 5). Specifically, results of the sub-analysis of PA measured with questionnaires showed that participants walking 100 or more minutes per week showed a 73% lower mortality risk, than those walking less than 100 minutes per week.

3.4 Publication bias

Visual inspection of funnel plots confirmed the presence of small-study effects for all subgroup analyses (figure S1, supplementary material). The Egger regression test for funnel plot asymmetry showed absence of bias for the work (p=0.290) sub-analysis but confirmed the presence of bias for

the 6MWT (p=0.005), VO_2 (p=0.005) and time in PA (p=0.007) sub-analyses. Moreover, the Begg rank correlation test showed absence of bias for all exercise capacity measures (6MWT, p=0.234; VO_2, p=0.327; work, p=0.099), excepting for the analysis of time spent in PA measured with accelerometry and questionnaires (p=0.042).

3.5 Subgroup analysis

Results of the 6MWT meta-analysis including only people with IPF were similar to the ones presented in the 6MWT meta-analysis for all ILD subtypes (figure 2); except the sub-analysis of 6MWD decrease over time, which showed that people with IPF presented a higher mortality risk [HR: 3.58 95%CI (2.79; 4.59) *vs.* 2.95 (1.90; 4.58) in figure 2] and this analysis was associated with a lower heterogeneity (I^2: 0%, p=0.886 *vs*. I^2: 78.9%, p<0.001) than overall people with ILD (Figure S2, in supplementary material).

Results of the fixed effects model showed almost no differences in the 6MWT meta-analysis, except for the sub-analysis of 6MWD decrease, in which a reduction in the subtotal was observed [HR: 2.10 95%CI (1.78; 2.47) *vs.* 2.95 (1.90; 4.58) in random effects model] (data not shown). No differences in VO_2 pooled effect size in comparison with random effects results were found (data not shown). A reduction in the overall pooled effect size in the work meta-analysis [HR: 0.96 95%CI (0.80; 0.93) *vs.* 0.88 (0.81; 0.96) in random effects model] and in the time spent in PA meta-analysis [HR: 0.97 95%CI (0.95; 0.98) *vs.* 0.79 (0.64; 0.93) in random effects model] was found, with similar heterogeneity (data not shown).

Excluding each study sequentially did not modify results of the VO_2, work and time spent in PA meta-analyses. However, in the 6MWT meta-analysis excluding the non-significant study of Lama et al. 2003[27] was associated with a significantly increase in overall mortality risk (Figure S3, in supplementary material).

4. Discussion

This systematic review with meta-analysis showed that PA and exercise capacity was significantly associated with mortality risk in people with ILD. Most studies have used the 6MWT, while other PA and exercise measures such as VO_2, work and time spent in PA have been scarcely explored.

This work extends findings from earlier evidence by presenting for the first time a quantification of the association of several PA and exercise capacity measures and mortality risk in people with ILD using a meta-analytical approach.

Our meta-analysis found that the distance walked and/or a decrease≥26m in the six-minute walking distance over time are strong indicators of mortality in people with ILD. Specifically, individuals walking less than 250m had more than a twofold higher mortality risk compared to those walking 350m or more. These results are in line with a previous work of the European Respiratory/American Thoracic Societies suggesting that a distance of 254m in the 6MWT is associated with increased mortality risk in people with ILD [12]. A review on the value and application of the 6MWT in IPF also found a significant association between a 6MWD lower than 250m and a twofold higher mortality risk, recommending this threshold to assess prognosis and predict survival in this population [13]. Individuals with a 6MWD between 250-350m also presented a twofold higher mortality risk. However, the use of the threshold of 350m in people with ILD is not so common, despite its widely application in people with COPD. This might be explained by the different cut-offs proposed in the literature (i.e., 6MWD<300m [17,45], <330m [59], <350m [19] or between 250-350m [6,18,31]) and the lack of consensus about which one is more appropriate to predict mortality.

Moreover, a decrease in the 6MWD≥26m over time (6-48 months) was associated with an almost threefold (HR: 2.95) higher mortality risk. This estimate increases (HR: 3.58) when the analysis only includes people with IPF. These findings highlight the implications of the decline in functional exercise capacity over time on mortality risk of people with ILD; and alert for the importance of maintaining these individuals physically active to delay premature mortality [41]. In participants walking more than 350m, we observed that an increase of 50m over time was associated with a 20%

lower mortality risk, which might be considered a protective factor. Establishing protective factors in people with ILD is crucial, and improvement in exercise capacity, which is a modifiable risk factor, is a step towards slowing disease progression and delaying premature death [3].

The VO_2 overall estimate was associated with a 10% lower mortality risk. A previous systematic review [60] showed that the evidence to confirm the value of the cardiopulmonary exercise test, namely the VO_2, as a predictor of mortality in people with ILD is poor, due to the scarcity of studies on this topic, their low methodological quality and the existence of high levels of heterogeneity [60]. Thus, our findings might contribute to expand evidence on the importance of cardiopulmonary exercise tests to predict mortality, but further research is needed.

We also found that an increase of 10-20W or 10% predicted in work was associated with about 8 to 12% lower mortality risk in people with ILD. Work measures are associated with functional exercise capacity decline and muscle weakness [28], and the deleterious effects of ILD in muscle function seem to have important negative effects on disease progression and mortality [28]. Thus, our findings emphasize the urgent need of investments to ensure access to personalized evidence-based interventions aiming to improve exercise capacity, functional status, and muscle strength in people with ILD, e.g., pulmonary rehabilitation. In fact, growing evidence has been showing that pulmonary rehabilitation improves exercise capacity, dyspnoea and quality of life in people with ILD [61], thus showing potential to contribute for preventing premature mortality in this population.

Time spent in PA assessed with accelerometry and questionnaires was associated with a 45% lower mortality risk. PA might constitute an important indicator of mortality in people with ILD, since it represents a clinically meaningful surrogate of a patient's well-being and everyday functional status [46]. Nevertheless, caution in this interpretation is recommended for two main reasons. Firstly, there are still few studies supporting the association of most PA measures and mortality risk, highlighting the need of further research including large cohorts of people with ILD. Secondly, both objective [8,46] and subjective [44] measures were described in the literature and some misclassification might exist. For instance, our results showed that walking time was strongly associated with mortality risk, but

the amount of PA was collected by questionnaires which might have led to under- or overestimation and might be subject to recall bias and social desirability effect. Efforts have been made to demonstrate the validity, reliability, and clinical interpretability of the PA questionnaires in people with ILD since their results showed to be strongly correlated with accelerometry parameters, daily steps, and health-related quality of life, but further research is needed for developing evidence-based PA guidelines for people with ILD.

Finally, our findings showed that the association between PA and exercise capacity measures and mortality risk was mostly reported in people with IPF (84% of the sample). Specifically, the sub-analysis of 6MWD<250m and the meta-analysis of time spent in PA only included people with IPF which might have influenced our results towards a higher mortality risk. IPF is the most prevalent ILD and presents the worst prognosis with a median survival of 2 to 5 years after diagnosis, thus these findings are important, but also stress the need of further studies including other people with non-IPF ILD subtypes.

Methodological considerations

This systematic review including meta-analysis has a number of limitations that need to be acknowledged. Moderate to high heterogeneity between studies was found, which reduced the power to detect statistically significant differences and limited comparisons. To account for this heterogeneity, both fixed and random effects models were tested and the last were computed as main analyses since they provided more precise and balanced estimates in which large studies are less likely to dominate the analysis and small studies are less likely to be underestimated.

A potential source of selection bias might have emerged because only studies with extractable and comparable results were considered in the meta-analysis. Our summary estimates might be overestimating the strength of the association between PA and exercise measures and mortality risk, confirmed by the presence of publication bias in the visual inspection of funnel plots, since studies with negative results are less frequently published [12]. The assessment of both physical activity/exercise capacity and mortality risk might have been subjected to measurement bias (i.e.,

measurement error in the assessment of PA/exercise capacity and mortality risk), which could have impacted the results of the included studies. Additionally, the quality of the figures produced in the meta-analysis depended on the PA and exercise estimates and ranges therefore, some standardization in collection and reporting of these measures would strengthen our results. Nevertheless, as the meta-analysis included about 50% of the studies, provided confidence in our results. The number of participants with non-IPF ILD was significantly low, which prevent us of conducting subgroup analyses for other ILD subtypes, reinforcing the need for further studies measuring the association of PA/exercise capacity measures and mortality risk in non-IPF patients. Finally, our search only included indexed databases thus, data of unpublished work or grey literature were not included.

5. Conclusions

Physical activity and exercise capacity measures show a consistent and quantifiable association with mortality risk, demonstrating to be important indicators of mortality in people with ILD. Our findings reinforce the use of these measures in clinical practice for setting prognosis and predicting survival. The 6MWT has been extensively used to assess exercise capacity in people with ILD, and there are already established thresholds for mortality risk in this population therefore, the 6MWT shows high potential to be used as a predictor of mortality in clinical practice.

Evidence on the use of other measures namely VO_2, work and daily PA is promising but still scarce and thus, additional research is required. Our findings indicate that a cut-off of 250m or a decrease ≥26m in the 6MWT over time could be considered in clinical settings to support diagnosis, prognosis, and decision-making on personalized interventions for improving PA and exercise capacity, and ultimately reducing premature mortality in people with ILD.

Practical implications:

- Physical activity (PA) and exercise measures are associated with mortality risk in people with ILD.
- The 6-minute walk test (6MWT) has been widely used to assess exercise capacity in people with ILD, with established thresholds for mortality risk thus, it shows potential to be use as a predictor of mortality in clinical practice.
- People with ILD walking less than 250m in the 6MWT, or with a decrease in walking distance ≥26m over time (6-48 months) showed a twofold and threefold higher mortality risk, respectively.
- Association of other measures (VO_2, work and time in PA) with mortality risk is still unclear.
- Interventions to improve PA and exercise capacity may have potential to delay premature mortality in people with ILD. The cut-off of 250m or a decrease ≥26m in the 6MWT over time (6-48 months) should be considered in clinical settings to support diagnosis, prognosis, and decision-making on interventions for people with ILD.

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Figure 1: Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) flow diagram of the literature search (adapted from Page et al. 2021).

Figure 2: Forest plot of hazard ratios (HR) for the association of six-minute walk test (6MWT) and mortality in people with interstitial lung disease (ILD). Weights are from random-effects; IPF: Idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease-associated interstitial lung disease; UIP: usual interstitial pneumonia; 6MWD: six-minute walk distance; Ref.: reference category.

Figure 3: Forest plot of hazard ratios (HR) for the association of peak oxygen uptake (VO_2 peak) and maximal oxygen uptake (VO_2 max) and mortality in people with interstitial lung disease (ILD). Weights are from random-effects; IPF: Idiopathic pulmonary fibrosis; SSc-ILD: systemic sclerosis-associated interstitial lung disease; Ref.: reference category.

Figure 4: Forest plot of hazard ratios (HR) for the association of work expressed in watts (W) and mortality in people with interstitial lung disease (ILD). Weights are from random-effects; IPF: Idiopathic pulmonary fibrosis; Ref.: reference category.

Figure 5: Forest plot of hazard ratios (HR) for the association of daily PA and mortality in people with interstitial lung disease (ILD). Weights are from random-effects; IPF: Idiopathic pulmonary fibrosis; Ref.: reference category; In Nishiyama et al. 2018, light activity refers to ~0.031 kcal/min/kg, moderate to ~0.083 kcal/min/kg, and vigorous to >0.083 kcal/min/kg of caloric expenditure.

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Declarations of interest: none.

Ethical Compliance:

The research was conducted in accordance with the 1964 Helsinki Declaration and ethical approval is not needed since this study is a literature review and did not directly include human participants.

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Objective: To summarize evidence on the association of PA and exercise capacity and mortality risk in people with ILD, and to quantify its magnitude by conducting a meta-analysis.

METHODS

Data Sources:

PubMed.gov Scopus WEB OF SCIENCE EBSCO

Up to September 2021

Data Extraction: authors independently screened studies, extracted data and assessed risk of bias with the **Newcastle–Ottawa Scale**.

Data analysis:

Primary outcome >> **overall mortality.**

Random-effects meta-analysis of logarithmic **hazard ratios.**

Heterogeneity was quantified using **I-squared statistic.**

Publication bias >> visual inspection of **funnel plots**.

RESULTS

52 studies were included with **10 349** people with ILD.

AGE **64±9years** **67%** ♂

78% idiopathic pulmonary fibrosis

Mean DLCO: 48.2±15.5%predicted

Most reported measures:

6 MINUTE WALK TEST — Oxygen uptake — Work in watts — Time spent in PA

Meta-analysis

3X **Higher mortality risk**

- **2X** — **6MWD 250-350 meters (m) vs. ≥350m**
- **2.5X** — **6MWD <250m vs. 300-350m**
- **6MWD decrease over time (>26m)**

An increase of 10-20W or 10%predicted **in work** → **12%**

Lower mortality risk

Time spent in PA (≥ 100min./week or ≥0.031kcal/min/kg/day) → **45%**

Physical activity and exercise capacity measures were associated with mortality risk in people with ILD.
Personalised interventions to improve PA should be considered to delay premature mortality in people with ILD.

Graphics Abstract

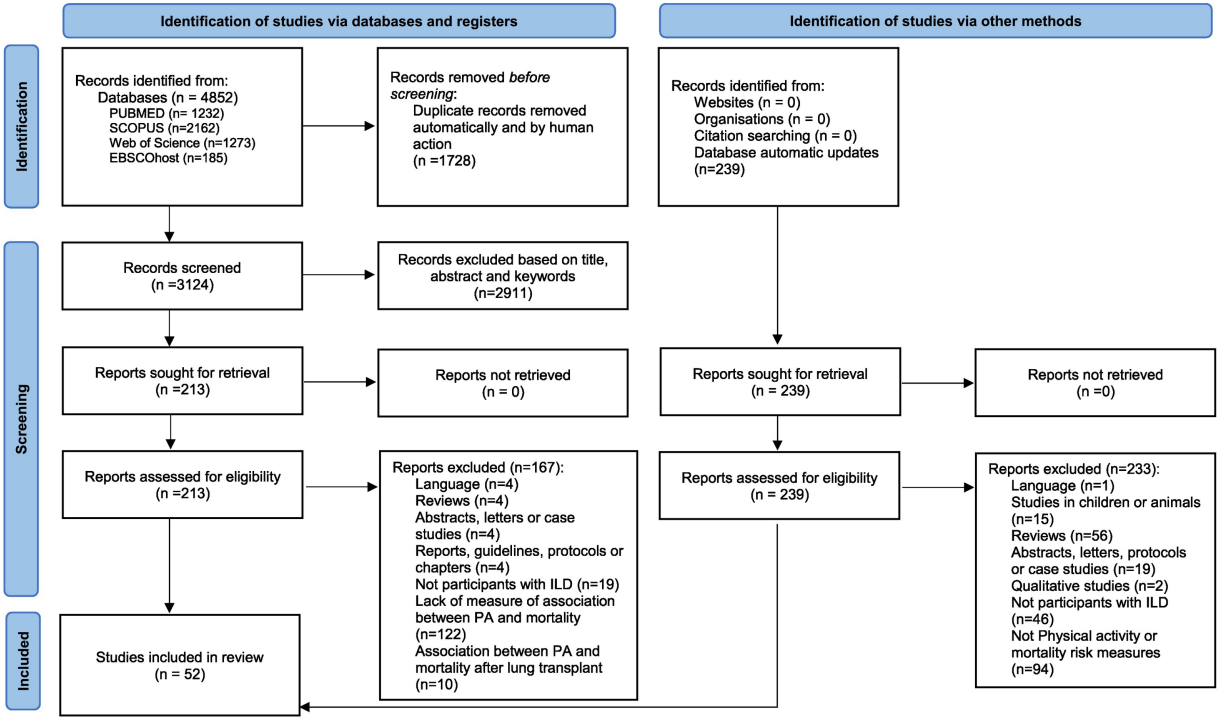
Identification of studies via databases and registers
Identification of studies via other methods
Identification
Screening
Included
Records identified from:
Databases (n = 4852)
PUBMED (n= 1232)
SCOPUS (n=2162)
Web of Science (n=1273)
EBSCOhost (n=185)
Records removed *before screening*:
Duplicate records removed automatically and by human action
(n =1728)
Records identified from:
Websites (n = 0)
Organisations (n = 0)
Citation searching (n = 0)
Database automatic updates
(n=239)
Records screened
(n =3124)
Records excluded based on title, abstract and keywords
(n=2911)
Reports sought for retrieval
(n =213)
Reports not retrieved
(n = 0)
Reports sought for retrieval
(n = 239)
Reports not retrieved
(n =0)
Reports assessed for eligibility
(n =213)
Reports excluded (n=167):
Language (n=4)
Reviews (n=4)
Abstracts, letters or case studies (n=4)
Reports, guidelines, protocols or chapters (n=4)
Not participants with ILD (n=19)
Lack of measure of association between PA and mortality
(n=122)
Association between PA and mortality after lung transplant
(n=10)
Reports assessed for eligibility
(n = 239)
Reports excluded (n=233):
Language (n=1)
Studies in children or animals
(n=15)
Reviews (n=56)
Abstracts, letters, protocols or case studies (n=19)
Qualitative studies (n=2)
Not participants with ILD
(n=46)
Not Physical activity or mortality risk measures
(n=94)
Studies included in review
(n = 52)

Figure 1

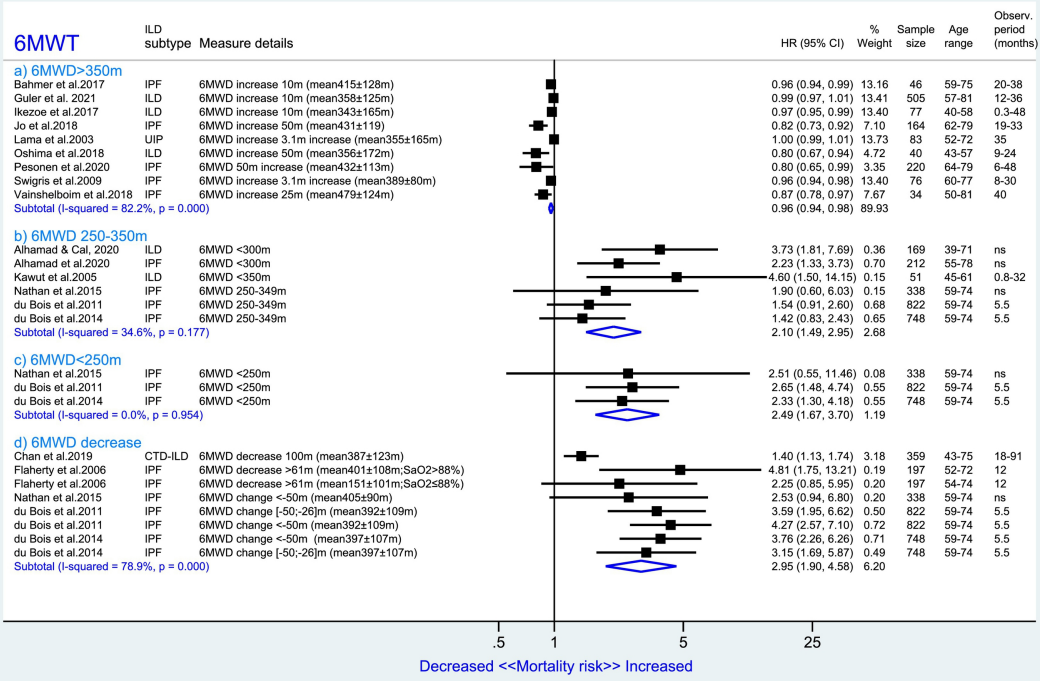
6MWT
ILD subtype
Measure details
HR (95% CI)
% Weight
Sample size
Age range
Observ. period (months)
a) 6MWD>350m
Bahmer et al.2017 IPF 6MWD increase 10m (mean415±128m) 0.96 (0.94, 0.99) 13.16 46 59-75 20-38
Guler et al. 2021 ILD 6MWD increase 10m (mean358±125m) 0.99 (0.97, 1.01) 13.41 505 57-81 12-36
Ikezoe et al.2017 ILD 6MWD increase 10m (mean343±165m) 0.97 (0.95, 0.99) 13.40 77 40-58 0.3-48
Jo et al.2018 IPF 6MWD increase 50m (mean431±119) 0.82 (0.73, 0.92) 7.10 164 62-79 19-33
Lama et al.2003 UIP 6MWD increase 3.1m increase (mean355±165m) 1.00 (0.99, 1.01) 13.73 83 52-72 35
Oshima et al.2018 ILD 6MWD increase 50m (mean356±172m) 0.80 (0.67, 0.94) 4.72 40 43-57 9-24
Pesonen et al.2020 IPF 6MWD 50m increase (mean432±113m) 0.80 (0.65, 0.99) 3.35 220 64-79 6-48
Swigris et al.2009 IPF 6MWD increase 3.1m increase (mean389±80m) 0.96 (0.94, 0.98) 13.40 76 60-77 8-30
Vainshelboim et al.2018 IPF 6MWD increase 25m (mean479±124m) 0.87 (0.78, 0.97) 7.67 34 50-81 40
Subtotal (I-squared = 82.2%, p = 0.000) 0.96 (0.94, 0.98) 89.93
b) 6MWD 250-350m
Alhamad & Cal, 2020 ILD 6MWD <300m 3.73 (1.81, 7.69) 0.36 169 39-71 ns
Alhamad et al.2020 IPF 6MWD <300m 2.23 (1.33, 3.73) 0.70 212 55-78 ns
Kawut et al.2005 ILD 6MWD <350m 4.60 (1.50, 14.15) 0.15 51 45-61 0.8-32
Nathan et al.2015 IPF 6MWD 250-349m 1.90 (0.60, 6.03) 0.15 338 59-74 ns
du Bois et al.2011 IPF 6MWD 250-349m 1.54 (0.91, 2.60) 0.68 822 59-74 5.5
du Bois et al.2014 IPF 6MWD 250-349m 1.42 (0.83, 2.43) 0.65 748 59-74 5.5
Subtotal (I-squared = 34.6%, p = 0.177) 2.10 (1.49, 2.95) 2.68
c) 6MWD<250m
Nathan et al.2015 IPF 6MWD <250m 2.51 (0.55, 11.46) 0.08 338 59-74 ns
du Bois et al.2011 IPF 6MWD <250m 2.65 (1.48, 4.74) 0.55 822 59-74 5.5
du Bois et al.2014 IPF 6MWD <250m 2.33 (1.30, 4.18) 0.55 748 59-74 5.5
Subtotal (I-squared = 0.0%, p = 0.954) 2.49 (1.67, 3.70) 1.19
d) 6MWD decrease
Chan et al.2019 CTD-ILD 6MWD decrease 100m (mean387±123m) 1.40 (1.13, 1.74) 3.18 359 43-75 18-91
Flaherty et al.2006 IPF 6MWD decrease >61m (mean401±108m;SaO2>88%) 4.81 (1.75, 13.21) 0.19 197 52-72 12
Flaherty et al.2006 IPF 6MWD decrease ≤61m (mean151±101m;SaO2≤88%) 2.25 (0.85, 5.95) 0.20 197 54-74 12
Nathan et al.2015 IPF 6MWD change <-50m (mean405±90m) 2.53 (0.94, 6.80) 0.20 338 59-74 ns
du Bois et al.2011 IPF 6MWD change [-50;-26]m (mean392±109m) 3.59 (1.95, 6.62) 0.50 822 59-74 5.5
du Bois et al.2011 IPF 6MWD change <-50m (mean392±109m) 4.27 (2.57, 7.10) 0.72 822 59-74 5.5
du Bois et al.2014 IPF 6MWD change <-50m (mean397±107m) 3.76 (2.26, 6.26) 0.71 748 59-74 5.5
du Bois et al.2014 IPF 6MWD change [-50;-26]m (mean397±107m) 3.15 (1.69, 5.87) 0.49 748 59-74 5.5
Subtotal (I-squared = 78.9%, p = 0.000) 2.95 (1.90, 4.58) 6.20
.5
1
5
25
Decreased <<Mortality risk>> Increased

Figure 2

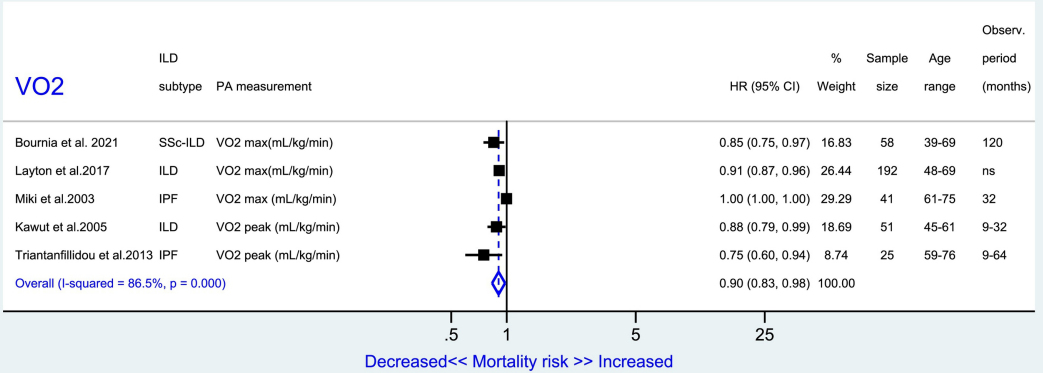
VO2
ILD subtype
PA measurement
HR (95% CI)
% Weight
Sample size
Age range
Observ. period (months)
Bournia et al. 2021 SSc-ILD VO2 max(mL/kg/min) 0.85 (0.75, 0.97) 16.83 58 39-69 120
Layton et al.2017 ILD VO2 max(mL/kg/min) 0.91 (0.87, 0.96) 26.44 192 48-69 ns
Miki et al.2003 IPF VO2 max (mL/kg/min) 1.00 (1.00, 1.00) 29.29 41 61-75 32
Kawut et al.2005 ILD VO2 peak (mL/kg/min) 0.88 (0.79, 0.99) 18.69 51 45-61 9-32
Triantanfillidou et al.2013 IPF VO2 peak (mL/kg/min) 0.75 (0.60, 0.94) 8.74 25 59-76 9-64
Overall (I-squared = 86.5%, p = 0.000) 0.90 (0.83, 0.98) 100.00
.5
1
5
25
Decreased<< Mortality risk >> Increased

Figure 3

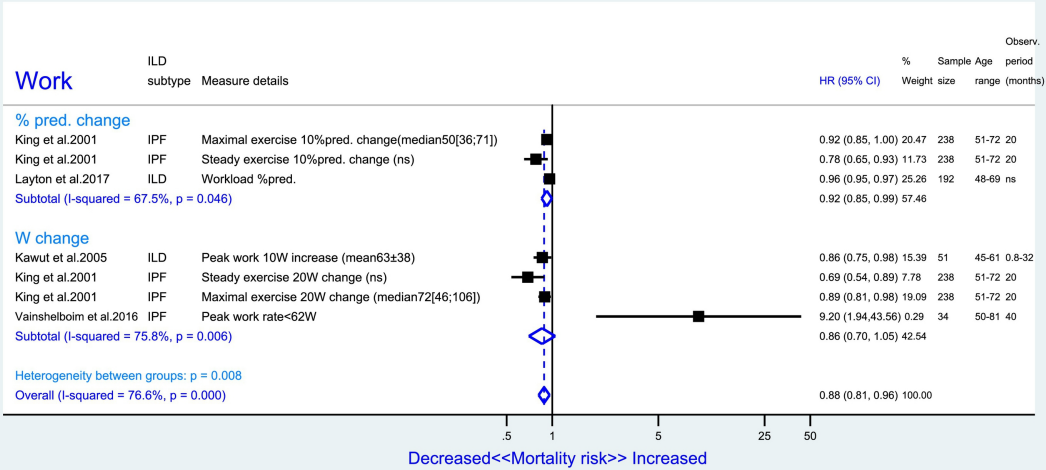
Work
ILD subtype
Measure details
HR (95% CI)
% Weight
Sample size
Age range
Observ. period (months)
% pred. change
King et al.2001 IPF Maximal exercise 10%pred. change(median50[36;71]) 0.92 (0.85, 1.00) 20.47 238 51-72 20
King et al.2001 IPF Steady exercise 10%pred. change (ns) 0.78 (0.65, 0.93) 11.73 238 51-72 20
Layton et al.2017 ILD Workload %pred. 0.96 (0.95, 0.97) 25.26 192 48-69 ns
Subtotal (I-squared = 67.5%, p = 0.046) 0.92 (0.85, 0.99) 57.46
W change
Kawut et al.2005 ILD Peak work 10W increase (mean63±38) 0.86 (0.75, 0.98) 15.39 51 45-61 0.8-32
King et al.2001 IPF Steady exercise 20W change (ns) 0.69 (0.54, 0.89) 7.78 238 51-72 20
King et al.2001 IPF Maximal exercise 20W change (median72[46;106]) 0.89 (0.81, 0.98) 19.09 238 51-72 20
Vainshelboim et al.2016 IPF Peak work rate<62W 9.20 (1.94,43.56) 0.29 34 50-81 40
Subtotal (I-squared = 75.8%, p = 0.006) 0.86 (0.70, 1.05) 42.54
Heterogeneity between groups: p = 0.008
Overall (I-squared = 76.6%, p = 0.000) 0.88 (0.81, 0.96) 100.00
.5
1
5
25
50
Decreased<<Mortality risk>> Increased

Figure 4

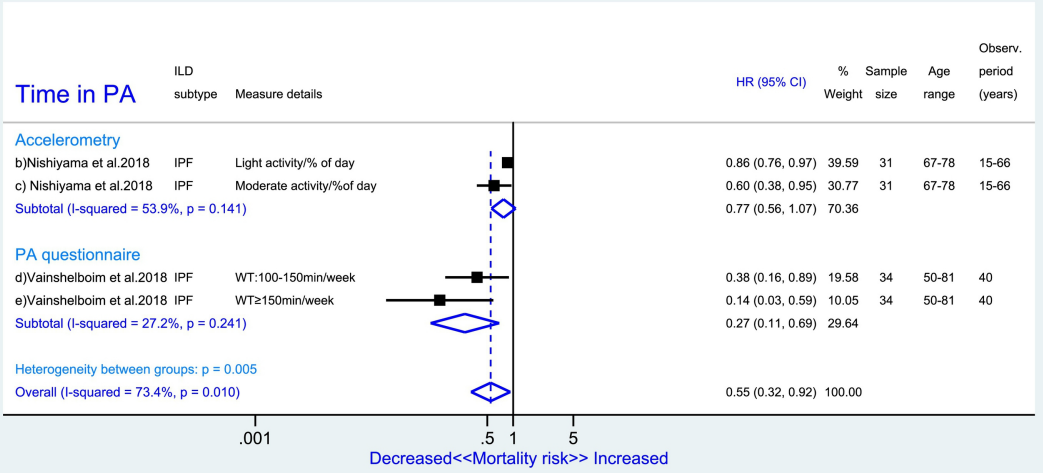
Time in PA
ILD subtype
Measure details
HR (95% CI)
% Weight
Sample size
Age range
Observ. period (years)
Accelerometry
b)Nishiyama et al.2018 IPF Light activity/% of day 0.86 (0.76, 0.97) 39.59 31 67-78 15-66
c) Nishiyama et al.2018 IPF Moderate activity/%of day 0.60 (0.38, 0.95) 30.77 31 67-78 15-66
Subtotal (I-squared = 53.9%, p = 0.141) 0.77 (0.56, 1.07) 70.36
PA questionnaire
d)Vainshelboim et al.2018 IPF WT:100-150min/week 0.38 (0.16, 0.89) 19.58 34 50-81 40
e)Vainshelboim et al.2018 IPF WT≥150min/week 0.14 (0.03, 0.59) 10.05 34 50-81 40
Subtotal (I-squared = 27.2%, p = 0.241) 0.27 (0.11, 0.69) 29.64
Heterogeneity between groups: p = 0.005
Overall (I-squared = 73.4%, p = 0.010) 0.55 (0.32, 0.92) 100.00
.001
.5
1
5
Decreased<<Mortality risk>> Increased

Figure 5