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Bridging The Regulatory-Payer Evidence Gap: A Case Study With Six Minute Walk Distance And Mortality

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Background and Objective

- Clinical outcomes such as exercise capacity are often accepted by regulators but not directly meaningful for payers or health technology assessment (HTA) bodies. Linking these outcomes to mortality can help bridge the evidence gap and strengthen payer value stories.
- **Objective**: To evaluate whether six-minute walk distance (6MWD) predicts mortality and demonstrate a methodology that can be applied across diseases.

Methods

- **Literature search**: A targeted literature review identified studies reporting the association between 6MWD and mortality in patients with chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), or heart disease (HD). Studies with sufficient data for effect size extraction were included.
- **Data extraction**: Hazard ratios (HRs) for mortality per 10-meter increase in 6MWD were extracted or recalculated as needed. Standard errors were also extracted. Study-level characteristics, including mean age, sex distribution, disease type, and follow-up length, were collected.
- **Meta-analysis:** HRs and standard errors were combined using a random-effects meta-analysis to account for heterogeneity across studies. Between-study heterogeneity was assessed using the I^2 statistic.
- **Meta-regression:** Analyses were performed to explore the impact of covariates (age, sex, disease type, follow-up length) on HR variability.
- **Sensitivity analysis:** Statistical outliers were identified using Galbraith plots and excluded to assess the robustness of the results.
- **Software:** All analyses were conducted in R (version 4.1.3) using the *meta* and *metafor* packages.

Results

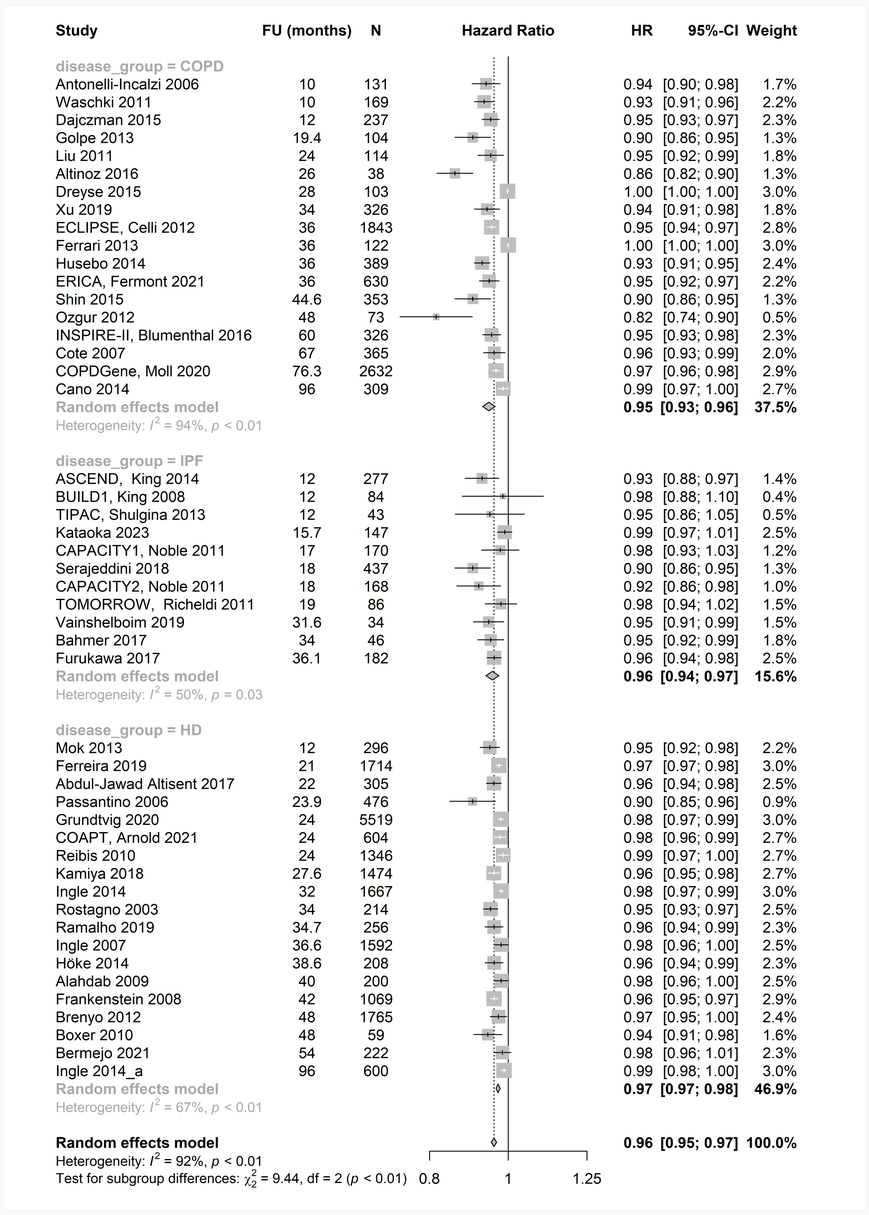
Study selection

- 63 records were initially identified; of those, 23 records were included. Of these 23 records, 3 were meta-analyses,[1-3] reporting on 27 studies in total; these 27 studies were also included.
- After de-duplication, 47 publications,[4-50] reporting on 48 individual studies, were included in our analysis.
  - 18 studies on COPD, 11 studies on IPF, 19 studies on HD (15 on heart failure, 1 on pulmonary hypertension and valvular heart disease, 1 on post-transcatheter aortic valve replacement, 1 on patients undergoing transcatheter aortic valve implantation, 1 on general cardiovascular disease).

Meta-analysis: Overall

- A 10-meter increase in 6MWD was significantly associated with reduced mortality risk, with a HR [95% CI; *P*-value] of 0.9601 [0.9529, 0.9674; $P < 0.01$].
- Sensitivity analysis excluding outliers[6,39] confirmed findings, with HR of 0.9632 [0.9568, 0.9697; $P < 0.01$].
- Between-study heterogeneity was high ($I^2 = 92\%$, $P < 0.01$) as shown in **Figure 1**.

Figure 1 Forest plot of overall meta-analysis



Results (cont'd)

Meta-analysis: By disease

- COPD: HRs ranged 0.82–1.00, showing a survival benefit; heterogeneity was high ($I^2 = 94\%$).
- IPF: HRs ranged 0.90–0.99 with moderate heterogeneity ($I^2 = 50\%$); two studies had wide CIs.
- Heart Disease: HRs ranged 0.90–0.99, indicating improved survival; heterogeneity was considerable ($I^2 = 67\%$).

Sensitivity analysis

- Exclusion of statistical outliers using Galbraith plots did not materially alter the findings, supporting the robustness of the meta-analysis results.

Meta-regression

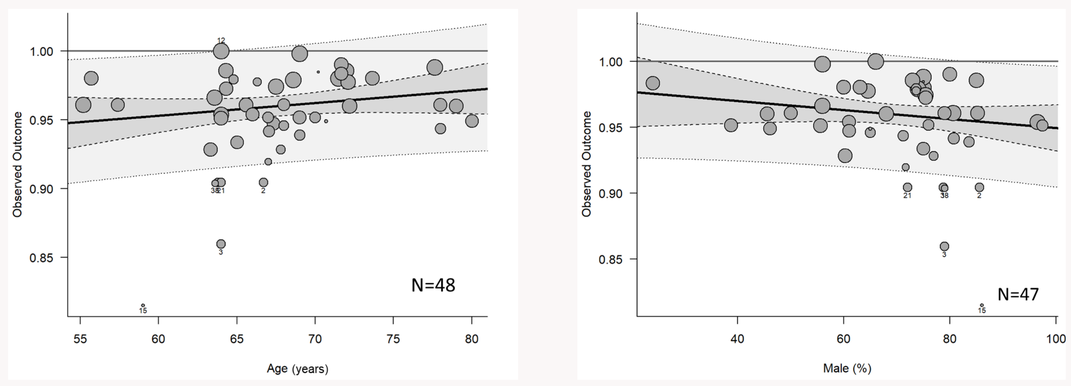
- Univariate analysis: Lower HRs observed in studies with younger participants and higher proportion of males (**Table 1**).
- Multivariate analysis: Age and heart disease subgroup were significant predictors; inclusion of covariates slightly reduced heterogeneity (**Table 1**).
- Predicted impact of 10-m increase in 6MWD (**Figure 2**):
  - Younger patients show a stronger mortality reduction than older patients, with a predicted HR [95% prediction interval] of 0.904 [0.822, 0.993] at 5 years, while the predicted HR is 0.953 [0.911, 0.997] at 60 years.
  - For male patients, an improvement in 6MWD is more relevant than for female patients since its impact on mortality is stronger, with a predicted HR of 0.949 [0.905, 0.996] for studies including only men, while it is 0.984 [0.928, 1.043] for studies including only female.

Table 1 Meta-regression

Univariate analysis				
Variable	Regression coefficient	Standard error	P-value	I^2
Age	0.0010	0.0007	0.1542	94.0%
Sex (male)	-0.0004	0.0003	0.1949	94.5%
Disease HD Disease IPF	0.0184 0.0048	0.0083 0.0115	**0.0274** 0.6798	94.3%
Length of follow-up	0.0003	0.0002	**0.0452**	94.1%

Multivariate analysis				
Variable	Regression coefficient	Standard error	P-value	I^2
Age	0.0055	0.0022	**0.0141**	87.9%
Disease HD	0.3813	0.1562	**0.0146**	
Disease IPF	0.0020	0.3074	0.9949	
Age: Disease HD	-0.0055	0.0023	**0.0195**	
Age: Disease IPF	-0.0000	0.0046	0.9944	

Figure 2 Regression with HR by age and sex



Circles: studies, with the size being reflective of the number of patients in the study. Black line: regression line. Dark grey shaded area: confidence interval. Light grey shaded area: prediction interval.

Limitations

- High heterogeneity across studies, and covariates such as age, disease type, and sex did not fully explain the observed between-study variability.
- Aggregate-data meta-regression has limited power.

Conclusions

- A 10-meter increase in 6MWD is associated with a 4% reduction in mortality risk (HR 0.96 [0.96–0.97], p<0.0001) across COPD, IPF, and heart disease. Sensitivity analyses excluding outliers confirmed the robustness of this association. Univariate meta-regression indicates stronger effects in younger and male patients, suggesting improvements in 6MWD are particularly relevant in these subgroups.
- This methodology provides a framework to link functional outcomes like 6MWD to survival, supporting value assessments for payers and HTA bodies.

Abbreviations

6MWD: six-minute walk distance,: CI: confidence interval, COPD: chronic obstructive pulmonary disease, FU: follow-up, HD: heart disease, HR: hazard ratio, HTA: health technology assessment, IPF: idiopathic pulmonary fibrosis,

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