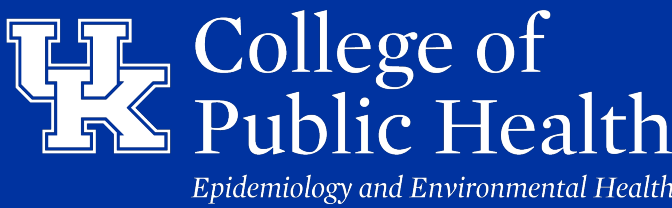


Digital Cognitive Prescreening in Alpha-1 Antitrypsin Deficiency: Associations with Dyspnea Severity, Age, and Education

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Introduction

- Cognitive impairment is increasingly recognized in chronic obstructive pulmonary disease (COPD), affecting memory, attention, and executive function.
- However, cognitive outcomes in alpha-1 antitrypsin deficiency (AATD), a genetic condition associated with early-onset COPD, remain poorly characterized.
- XpressO is a self-administered digital cognitive prescreening tool validated against the Montreal Cognitive Assessment (MoCA), assessing memory, executive function, and processing speed.

Methods

- The Study of Cognitive Outcomes: Perception and Evaluation (SCOPE) enrolled individuals with AATD through AlphaNet, a U.S. health management organization between December 2025 and April 2026.
- Cognitive performance was assessed using XpressO scores (range 0-100) and categorized as low (≤ 42), intermediate (43-71), or high (≥ 72) (Figure 1).
- Shortness of breath (dyspnea) was evaluated using the modified Medical Research Council (mMRC) scale; health status was assessed using the Chronic Airways Assessment Test (CAAT).
- Cross-sectional associations with demographic and clinical characteristics were examined using correlation analyses and multivariable linear regression.

Results (unadjusted)

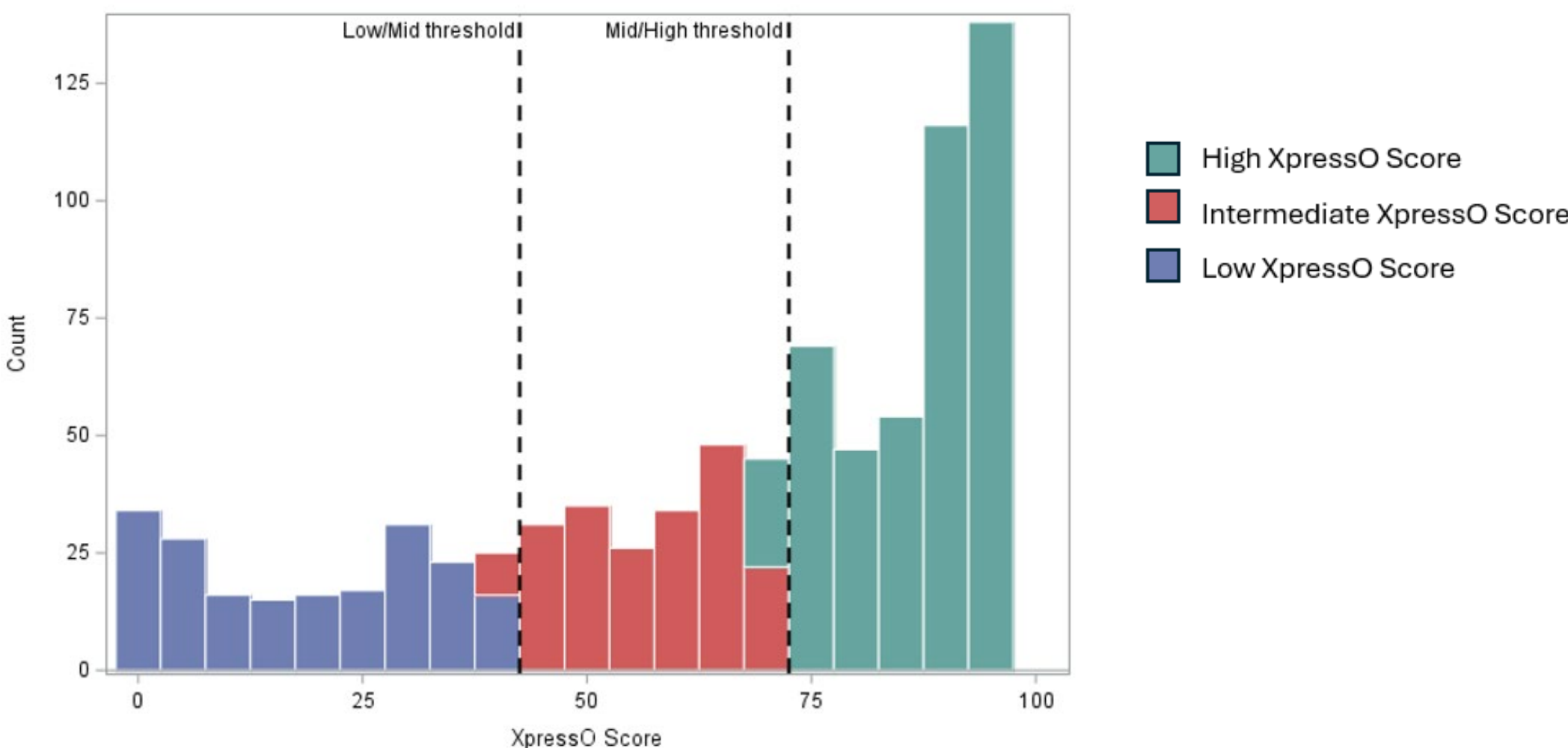
- Table 1 summarizes participant characteristics.
- Females had higher XpressO scores than males (69.0 vs 61.2; $p=0.0001$) and shorter completion times (5.1 vs 5.5 minutes; $p=0.0002$).
- Age was inversely correlated with XpressO score ($r = -0.20$; $p < 0.0001$), and longer test duration was also associated with lower performance ($r = -0.27$; $p < 0.0001$).
- Education was modestly positively correlated with XpressO score ($r = 0.10$; $p = 0.006$).
- Higher dyspnea burden (mMRC ≥ 2) and respiratory symptom burden (CAAT ≥ 10) were associated with lower XpressO (Figure 2).

Results (adjusted)

In multivariable linear regression:

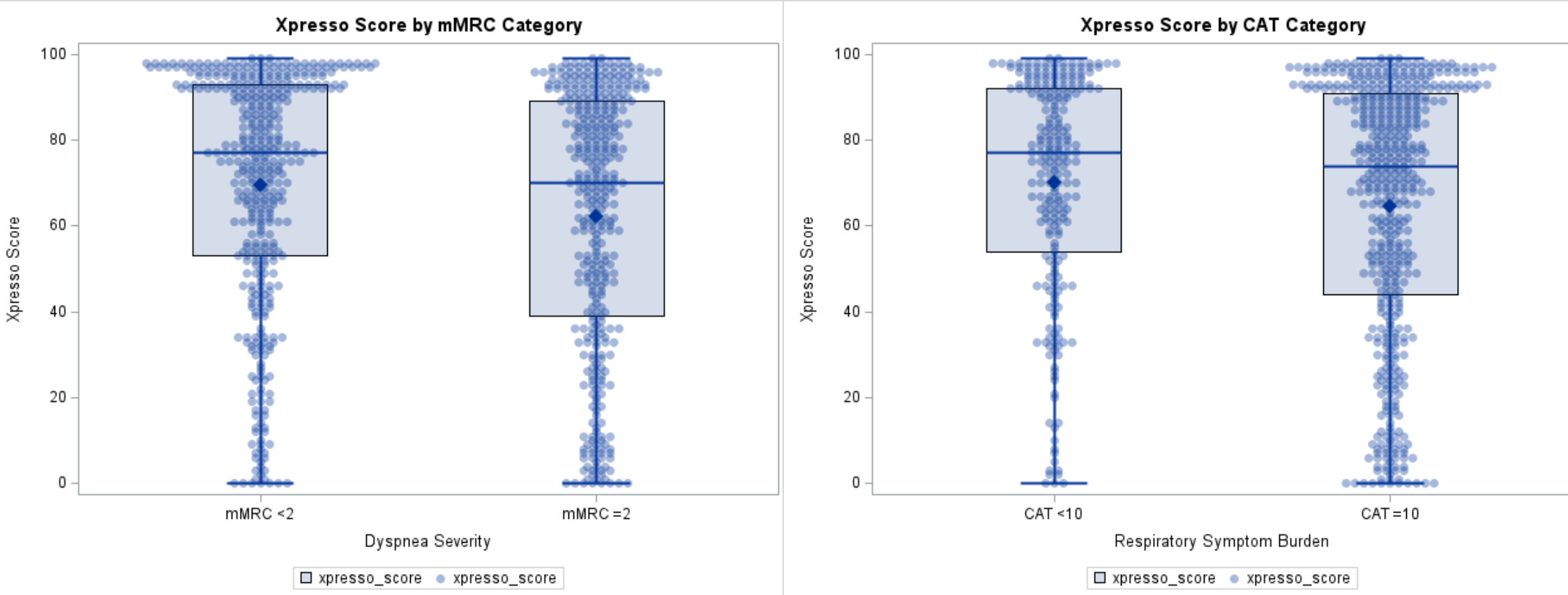
- mMRC ≥ 2 was independently associated with lower XpressO scores ($\beta = -5.79$; $p = 0.006$).
- CAT ≥ 10 was not independently associated with XpressO score ($p = 0.16$).
- Older age was associated with lower XpressO scores ($\beta \approx -0.5$ per year; $p < 0.001$).
- Female sex and higher education were associated with higher XpressO scores (both $p \leq 0.01$).

Figure 1. Distribution of XpressO scores according to their categorical levels



Overall, 23% had low (≤ 42), 24% intermediate (43-71), and 53% high (≥ 72) XpressO scores.

Figure 2. Unadjusted associations between XpressO scores and respiratory symptom burden



Higher dyspnea burden (mMRC ≥ 2) and respiratory symptom burden (CAAT ≥ 10) were associated with lower XpressO scores. Mean XpressO scores were 69.4 vs 62.3 for mMRC <2 vs ≥ 2 ($p=0.0006$) and 70.0 vs 64.6 for CAT <10 vs ≥ 10 ($p=0.017$).

Table 1. Participant characteristics, n=855

Age, mean (SD), yrs	65.1 (10.4)
Female	520 (61.1)
Non-Hispanic White	818 (95.7)
Years of education, mean (SD), yrs (n=720)	15.4 (3.8)
XpressO score, mean (SD)	65.9 (29.1)
XpressO score category	
Low ≤ 42	196 (22.9)
Intermediate 43-71	204 (23.9)
High ≥ 72	455 (53.2)
XpressO test duration, mean (SD), min	5.2 (1.6)
CAAT score ≥ 10	506 (67.7)
N=747	
mMRC grade ≥ 2	381 (47.5)
n=802	
Severe AAT deficiency (ZZ, ZNull)	535 (62.6)

Data presented in n (%) unless otherwise noted. Chronic Airways Assessment Test (CAAT) score ≥ 10 (range 0-40) indicates high burden of chronic lung disease symptoms that significantly impacts daily life, functioning, and overall well-being. Modified Medical Research Council (mMRC) grade ≥ 2 (range 0-4) indicates clinically significant impact of breathlessness on daily activities.

Conclusions

- Cognitive performance in this AATD cohort showed substantial variability and was associated with age, education, sex, and test duration
- After adjustment for covariates, dyspnea severity (mMRC ≥ 2) remained independently associated with lower XpressO scores, whereas respiratory symptom burden (CAAT ≥ 10) was not.
- These findings suggest that dyspnea severity, rather than overall respiratory symptom burden, may be more closely linked to cognitive performance in AATD, and support the feasibility of digital cognitive screening in this population.

References

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