Title: Voluntary Cough Effectiveness and Airway Clearance in Neurodegenerative Disease

Authors: James C. Borders[1] & Michelle S. Troche[1]

Affiliation:

[1]Laboratory for the Study of Upper Airway Dysfunction, Department of Biobehavioral Sciences, Teachers College, Columbia University, New York, NY 10027, United States

Corresponding Author:

James C. Borders, MS, CCC-SLP

Laboratory for the Study of Upper Airway Dysfunction

Teachers College, Columbia University, New York City, NY, USA

Email: jcb2271@tc.columbia.edu

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Abstract:

Purpose: Voluntary cough dysfunction is highly prevalent across multiple patient populations. Voluntary cough has been utilized as a screening tool for swallowing safety deficits and as a target for compensatory and exercise-based dysphagia management. However, it remains unclear whether voluntary cough dysfunction is associated with the ability to effectively clear the airway.

Method: Individuals with neurodegenerative disorders performed same-day voluntary cough testing and flexible endoscopic evaluations of swallowing (FEES). Participants who were cued to cough after exhibiting penetration to the vocal folds and/or aspiration with thin liquids during FEES met inclusion criteria. One-hundred and twenty-three trials were blinded and the amount of residue before and after a cued cough on FEES was measured with a visual analog scale. Linear and binomial mixed effects models examined the relationship between cough airflow during voluntary cough testing and the proportion of residue expelled.

Results: Peak expiratory flow rate (p = .004) and cough expired volume from the entire epoch (p = .029) were significantly associated with the proportion of aspiration expelled from the subglottis. Peak expiratory flow rate values of 3.00 L/s, 3.50 L/s and 5.30 L/s provided high predicted probabilities that $\geq$ 25%, $\geq$ 50%, and $\geq$ 80% aspirate was expelled. Accounting for depth of aspiration significantly improved model fit (p < .001).

Conclusions: These findings suggest that voluntary cough airflow is associated with cough effectiveness to clear aspiration from the subglottis, though aspiration amount and depth may play an important role in this relationship. These findings provide further support for the clinical utility of voluntary cough in the management of dysphagia.

Introduction

Cough is a vital airway defense mechanism that expels secretions and/or foreign material from the upper and lower airways. Cough (dystussia) and swallowing (dysphagia) dysfunction are known to frequently co-occur in many patient populations, including Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, stroke, and head and neck cancer (Hegland et al., 2014; Hutcheson et al., 2017; Pitts et al., 2008; Plowman et al., 2016; Silverman et al., 2016; Smith Hammond et al., 2009; Troche et al., 2016). Effective functioning of cough and swallowing, as well as other pulmonary defense mechanisms such as mucociliary clearance, intact immune responses, and oral hygiene, are important in preventing adverse health outcomes such as pneumonia (Bianchi et al., 2012; Happel et al., 2004; Langmore et al., 1998; Nicod, 1999).

The neural control of cough exists along a continuum with reflexive and volitional control at either end. Reflex cough is initiated in response to activation of airway sensory receptors which can include aspirate material or tussigenic stimuli like capsaicin or citric acid administered in laboratory settings. On the other hand, voluntary cough is initiated on command. In the presence of a sensory stimulus, individuals can volitionally modulate reflex cough motor output with higher-level cortical processing (Hegland et al., 2012). Both reflex and voluntary coughs result in a rapid expulsion of air which can be measured from either a gold-standard spirometer or handheld peak flow meter. Though both cough types share peripheral anatomy and physiology, there are distinct differences in their underlying neural substrates and sensorimotor control. Reflex cough is primarily mediated by the brainstem, whereas voluntary cough is reliant on cortical structures (Mazzone et al., 2009). Voluntary and reflex cough can be further classified as either single or sequential with changes to cough airflow and effectiveness based on the number of coughs produced. Single coughs are thought to be important for removing material from the upper airway and trachea, whereas sequential coughs are effective at removing material from lower airway structures, including the mainstem bronchi, due to dynamic compression from a decrease in cross-sectional area (Ross et al., 1955). In combination with lower lung volumes, this transfers equal pressure points resulting in increased airflow velocity and improved clearance at different levels of the airway (Hegland et al., 2013). Several expiratory airflow measures are used to quantify the production of these shearing forces during cough and include parameters related to strength (e.g., peak expiratory flow rate, cough volume acceleration) and volume (e.g., cough expired volume).

Failure to clear the airway of secretions has been associated with an increased risk of lung infection (Dickey, 2018). Management of this airway encumbrance can be assisted by measuring voluntary cough dysfunction. In patients with neuromuscular respiratory insufficiency, voluntary cough airflow has predicted successful extubation and tracheostomy tube decannulation (Bach & Saporito, 1996; Khamiees et al., 2001), clearance of secretions (Boitano, 2006; Szeinberg et al., 1988), and response to cough-augmentation techniques (Toussaint et al., 2009). These studies suggest that voluntary cough airflow, specifically peak expiratory flow rate, is associated with secretion mobilization and removal from the airway in medically acute populations – supporting the role of voluntary cough in a patient’s ability to maintain a clear and patent airway.

Beyond understanding airway patency and secretion clearance post-extubation, voluntary cough assessments also play an important role in the management of patients with dysphagia and impaired swallowing safety. A subjective impression of voluntary cough function has been a long-standing aspect of clinical swallowing evaluations (Logemann, 1999). However, aerodynamic measures of voluntary cough function have only recently been used to objectively quantify airflow during swallowing assessments (Silverman et al., 2016; Watts et al., 2016). A growing body of literature has not only confirmed that voluntary cough dysfunction is highly prevalent in many patient populations compared to healthy controls (e.g., Ebihara et al., 2003; Kubo et al., 2020; Tabor-Gray et al., 2019), but that voluntary cough airflow dysfunction is related to swallowing dysfunction, such that outcomes like peak expiratory flow rate and cough volume acceleration are markedly reduced in patients with a greater degree of airway invasion (Pitts et al., 2008; Plowman et al., 2016; Silverman et al., 2016; Smith Hammond et al., 2001). In fact, recent studies suggest that voluntary cough may be a useful, low-cost screening tool to improve the identification of patients at risk for dysphagia (Pitts et al., 2010; Plowman et al., 2016; Smith Hammond et al., 2001). Collectively, these studies suggest that voluntary cough dysfunction is not only highly prevalent, but also a clinically relevant component of assessment and screening procedures for patients with dysphagia. However, it remains unclear whether voluntary cough dysfunction directly translates to compromised airway clearance of penetrant or aspirate material in patients with dysphagia.

Voluntary cough is also a common target for compensation and treatment in patients with dysphagia. From a compensatory perspective, voluntary cough is often prescribed as a strategy to promote clearance of penetrant or aspirate material from the airway in order to maintain a homeostatic pulmonary environment despite airway invasion during swallowing (Dickey, 2018; Hasani et al., 1994). However, this strategy requires intact voluntary cough functioning, which is often reduced in patients with dysphagia (Pitts et al., 2008; Plowman et al., 2016; Silverman et al., 2016; Smith Hammond et al., 2001). Recently, strength and skill-based treatments have shown preliminary efficacy to improve voluntary cough effectiveness, supporting its feasibility as a treatment target (Chiara et al., 2006; Curtis et al., 2020; Kim et al., 2009; Pitts et al., 2009). However, it remains unclear how voluntary cough airflow translates to functional outcomes, such as airway clearance. Clinically meaningful voluntary cough treatment targets would enable clinicians and patients to have a better understanding of rehabilitation goals and allow individualized, patient-centered approaches. For researchers, knowing clinically meaningful targets for voluntary cough effectiveness would allow for more adequate determinations of statistical power, thereby improving data collection efficiency and the quality of inferences from studies seeking to rehabilitate voluntary cough dysfunction.

Given the aforementioned gaps in our understanding of voluntary cough, this retrospective study aimed to determine clinically meaningful cut-off values for voluntary cough airflow associated with airway clearance. To this end, we first explored the relationship between voluntary cough airflow measures obtained during spirometry and the proportion of penetration or aspiration expelled from a cued voluntary cough during flexible endoscopic evaluations of swallowing (FEES). We hypothesized that higher cough airflow values would be associated with a greater percentage of material cleared during a cued cough on FEES. Next, we examined the ability of voluntary cough variables to predict “effective” airway clearance across four binary categorizations: ≥ 25%, ≥ 50%, ≥ 80%, and 100% residue expelled. We hypothesized that cough variables would discriminate between these categorizations and provide cut-off values with high predicted probabilities, sensitivity, and specificity. We also explored the effect of aspiration location (i.e., depth) on airway clearance and hypothesized that an interaction between aspiration location and cough airflow variables would influence the proportion of residue expelled.

Methods

Participants

This retrospective study included patients with neurodegenerative disease and suspected oropharyngeal dysphagia referred by Movement Disorders neurologists to an academic outpatient research clinic for evaluation of swallowing and cough function via FEES and spirometric voluntary cough testing. Data from these clinical evaluations were collected to determine eligibility for larger prospective cohort studies. Informed consent was obtained prior to enrollment and ethical approval was granted by the local Institutional Review Board. Inclusion criteria required (1) penetration to the level of the vocal folds without immediate ejection (penetration-aspiration scale score of 5) and/or aspiration without immediate ejection (penetration-aspiration scale scores 7 – 8) during FEES with thin liquids (Rosenbek et al., 1996), (2) a clinician cued voluntary cough after penetration and/or aspiration on FEES, (3) adequate visualization of the vocal folds and/or subglottis before and after the cued cough, and (4) voluntary cough testing via spirometry performed prior to FEES. All participants with Parkinson's disease were in the 'on' phase of their medication cycle during cough and swallowing assessments.

Voluntary Cough Testing

Three trials of sequential voluntary cough testing were performed prior to the swallowing evaluation. A facemask coupled to a pneumotachograph and digital spirometer (MLT 1000, ADInstruments, Inc.) was positioned over the participant's nose and mouth. Participants were provided the following instructions: "When you are ready, cough as if something has gone down the wrong pipe." The examiner also provided a model of a three-cough epoch. The number of coughs per trial was not standardized across participants. Airflow data were inputted to a Power

Lab Data Acquisition System (ADInstruments, Inc. version 8.1), digitized, and recorded to a computer. Each sample was low pass filtered at 50 Hz.

Flexible Endoscopic Evaluations of Swallowing

FEES were performed with a 3 mm diameter flexible distal chip laryngoscope (ENT-5000; Cogentix Medical, New York, USA) without the use of topical anesthetics or vasoconstrictors. Participants were presented with a variety of thin liquid bolus volumes, including 5 mL, 10 mL, 20 mL, 90 mL, and patient preferred volumes. All boluses were dyed with either barium, white, blue, or green dye to maximize visualization. In the presence of penetration and/or aspiration, clinicians provided cues for the patient to perform a voluntary cough. Given the retrospective nature of this study, the instruction and frequency of these cues was not standardized across patients.

Data Analysis

Video segments before and after the cued cough were de-identified and randomized. Raters were blinded to whether the video segment occurred before or after the cued cough. Additionally, segments did not include the cued cough in order to reduce rater bias. The number of coughs performed during FEES, a description of the clinician cue, and the location of penetration or aspiration were documented separately by a blinded rater. A qualitative description of location and depth was provided for each penetration and aspiration event. Specifically, four locations were used to describe penetration events: left and right anterior $1/3^{rd}$ and/or left and right posterior $2/3^{rd}$ of the vocal folds. Three locations were used to describe aspiration events: superior $1/3^{rd}$ of the subglottis shelf (i.e., “superior subglottis”), inferior $2/3^{rd}$

of the subglottis shelf (i.e., "inferior subglottis"), or inferior to the first ring of the cricoid cartilage (i.e., "trachea"; Figure 1). These categorical descriptors were used to further describe the data but were not used as an outcome in inferential statistical analyses. The proportion of residue expelled (based on VASES and described below) served as the primary outcome.

Outcome Measures

Raters used a 100-point visual analog scale and anatomic boundaries outlined in the Visual Analysis of Swallowing Efficiency and Safety (VASES) rating method to estimate the amount of penetrant and aspirate material present in each FEES video segment (Curtis et al., 2021). This rating reflected the amount of residue normalized to the area of the vocal folds or subglottis. Once ratings were unblinded, the proportion of residue expelled was individually calculated for each anatomic landmark (i.e., vocal folds, subglottis) by subtracting visual analog scale scores from before the cued cough to VAS after the cued cough and then dividing by the amount of residue present before the cough.

$$\text{Proportion of Material Expelled} = \frac{\text{VAS Before Cough} - \text{VAS After Cough}}{\text{VAS Before Cough}}$$

In instances where the visual analog scale rating was greater after the cued cough (e.g., cough resulted in more material entering the area of interest), a score of 0% residue expelled was assigned. Cough airflow variables measured from spirometric voluntary cough testing included peak expiratory flow rate (L/s), cough expired volume (L), and cough volume acceleration (L/s/s). These measures were obtained from the first cough in a cough epoch for each trial. Cough expired volume across the entire epoch (L) was also examined. The maximum cough airflow value for each cough variable across trials was used in order to capture the patient's best cough performance. The number of coughs (CrTot) from the maximum trial for each cough variable was included as a covariate.

Statistical Analysis

Linear mixed effects models were performed for each cough airflow variable with separate models for penetration and aspiration events. The proportion of residue expelled was the dependent variable, a cough airflow variable was the fixed effect, and participant was the random effect. Covariates included sex, number of coughs during FEES, and number of coughs during spirometric voluntary cough testing. We included the number of coughs during FEES and spirometry due to the known relationship between expiratory airflow and number of coughs (Hegland et al., 2013). We also included sex as a covariate to account for potential differences in tracheal area (Dominelli et al., 2018). Variance inflation factors (VIF) were calculated for each model. Fixed effects were deemed appropriate based on an a priori threshold (VIF < 3). The Akaike information criterion was used to determine the appropriate covariance structure. A compound symmetry covariance structure was used across all linear mixed effects models.

Binomial mixed effects models were also performed to explore the ability of cough variables to discriminate between "effective" and "ineffective" airway clearance while controlling for the aforementioned covariates. The random and fixed effects were identical to previously described linear mixed effects models. We explored four binary categorizations for expelling residue: (1) ≥ 25%, (2) ≥ 50%, (3) ≥ 80%, and (4) 100% residue expelled from the vocal folds or subglottis. Seventy-five percent was initially chosen as the third cut-off value; however, models failed to converge with this categorization. Additionally, all penetration and seven aspiration models failed to converge, likely due to overfitting and the data distribution, and were not reported. Specifically, the aspiration models that did not converge included cough expired volume from the first cough (≥ 50% and 100% residue expelled), cough volume acceleration (≥ 50% and 100% residue expelled), and cough expired volume from the entire epoch (≥ 25%, ≥ 50%, and 100% residue expelled). Predicted probabilities were calculated for each cough variable for statistically significant binomial models. Eighty percent predicted probability was determined a priori as providing "high" probabilities of effective airway clearance for cough airflow variables. Both linear and binomial mixed effects models were fit using restricted maximum likelihood estimation. Receiver operating characteristics (ROC) curves were also used to determine how well cough variables differentiated between "effective" and "ineffective" airway clearance. The area under the curve (AUC) was calculated to determine the probability that a cough airflow variable would adequately differentiate effectiveness of airway clearance. We considered an AUC of 0.7-0.8 as "adequate" and 0.8-0.9 as "excellent" (Copay et al., 2007). From ROC analyses, we obtained the cut-off value that maximized sensitivity and specificity, as well as values that prioritized either sensitivity or specificity. Both predicted probabilities and ROC analyses were provided since the former provides an assessment of the predictive nature of cough variables while controlling for the presence of covariates, whereas the latter evaluates how sensitivity and specificity varies based solely on cough cut-off values and may therefore be of greater clinical utility.

In order to examine the influence of aspiration location on the relationship between significant spirometric cough variables and the proportion of residue expelled, additional models were fit with the deepest location of aspiration as a main effect and then with a two-way interaction between aspiration location and peak expiratory flow rate. These models were each compared to the original model without either the main effect of aspiration location or two-way interaction. Models were fit using maximum likelihood estimation to allow for comparisons with likelihood ratio (LR) tests. The amount of unique variance explained (f^2) was used as a measure of effect size for continuous variables (Lorah, 2018). The amount of unique variance explained was obtained from marginal pseudo-R^2 for mixed models (Nakagawa & Schielzeth, 2013). Cohen's *d* was used as an effect size measure for categorical predictors (Westfall et al., 2014).

Simulation-based sensitivity power analyses were performed with the *simr* R package for the aforementioned models (Green & MacLeod, 2015). This was accomplished by inputting a range of effect sizes for the predictor (i.e., cough variable) of interest. Coefficients in binomial mixed models were exponentiated for interpretation as unstandardized odds ratios. Monte Carlo simulations were then performed to identify the minimum detectable effect size at 80% power. Results showed that aspiration linear mixed effects models had 80% power to detect $f^2 = 0.13$ for peak expiratory flow rate, $f^2 = 0.13$ for cough expired volume from the first cough, $f^2 = 0.10$ for cough expired volume from the entire epoch, and $f^2 = 0.14$ for cough volume acceleration (Appendix A). Model comparisons had 80% power to detect a main effect of $f^2 = 0.02$ for aspiration location, as well as a two-way interaction between peak expiratory flow rate and aspiration location of $f^2 = 0.78$.

Intraclass correlation coefficients (single measure, absolute agreement) were used to examine inter- and intra-rater reliability of visual analog scale residue ratings and cough variables for a randomized 20% of trials. Alpha was set at .05. Corrections for multiple comparisons were not used due to the exploratory nature of this study. Analyses were performed in R version 4.0.1 (R Core Team, 2018).

Results

Participant Demographics

Sixty-eight aspiration events across 33 participants met criteria for inclusion in this study (Figure 2). Aspiration events were from participants with a diagnosis of Parkinson’s disease (n = 26) or progressive supranuclear palsy (n = 7) (Table 1). Fifty-five penetration events across 30 participants were included. Participant diagnoses included Parkinson’s disease (n = 21), progressive supranuclear palsy (n = 2), multiple systems atrophy – cerebellar subtype (n = 2), and type 1 spinocerebellar ataxia (n = 2). Given the previously described analysis plan, aspiration and penetration events were analyzed separately and are therefore presented in two sections.

Aspiration

Trial Characteristics

Boluses were dyed with barium (51%), green (20%), blue (26%), and white dye (3%). Bolus volumes included 90 mL (50%), 20 mL (3%), 10 mL (31%), 5 mL (7%), and patient preferred (9%). Four aspiration trials (5.89%) demonstrated higher visual analog scale ratings after the cued cough and were assigned a rating of 0. Sixty-four percent of aspiration events had residue in the superior subglottis, 76% in inferior subglottis, and 31% in the trachea. Twenty-six percent of aspiration events were entirely cleared from the subglottis with a cued cough, 47% of coughs cleared at least 80% residue, 60% of coughs cleared at least 50% residue, and 12% of coughs did not clear any residue (0%). Among 18 aspiration events where residue was entirely expelled from the subglottis, the superior subglottis was the deepest location of aspiration for most events (56%), whereas the remaining 44% were in the inferior subglottis. Cough instructions included cues for a strong single cough (41%), multiple coughs (18%), both a strong and sequential cough (19%), or no qualifiers (22%). There were no significant differences in the proportion of aspiration expelled between types of cough cues ($p > .05$). There was a strong correlation between the amount of aspirate residue in the subglottis before and after the cued cough ($r = 0.90$, $p < .001$, Appendix B).

Peak Expiratory Flow Rate

Relationship Between Cough Airflow & Airway Clearance

Linear mixed effects models showed a significant main effect of peak expiratory flow rate ($p = .004$, $f^2 = 0.17$) on the amount of residue expelled from the subglottis when controlling for sex, number of coughs during FEES, and number of coughs during spirometry (Table 2). Binomial mixed effects models showed a significant main effect of peak expiratory flow rate to predict ≥ 25% residue expelled ($p = .018$, $OR = 3.47$), ≥ 50% residue expelled ($p = .033$, $OR = 3.63$), and ≥ 80% residue expelled ($p = .015$, $OR = 2.10$) while controlling for covariates (Table 3). However, peak expiratory flow rate did not significantly discriminate between airway clearance of 100% residue ($p = .056$, $OR = 1.80$, Appendix C).

Predictive Ability of Peak Expiratory Flow Rate

Predicted probabilities of 3 L/s, 3.50 L/s, and 5.30 L/s peak expiratory flow rate were observed for clearance of ≥ 25%, ≥ 50%, and ≥ 80% residue from the subglottis, respectively, when controlling for covariates (Figure 4). ROC analyses demonstrated adequate AUC values (> 0.70) for clearance of ≥ 25% and ≥ 50% residue, suggesting that peak expiratory flow rate adequately differentiated between "effective" and "ineffective" airway clearance with optimal cut-off values of 3.23 L/s and 2.97 L/s, respectively (Figure 5).

Effect of Aspiration Location

Model comparisons showed that including aspiration location significantly improved model fit ($p < .001$, $LR = 32.74$). The full model showed a significant main effect of aspiration location ($p < .001$, $f^2 = 0.58$), whereas peak expiratory flow rate was non-significant ($p = .087$, $f^2 = 0.08$). Pairwise comparisons showed significant differences in the proportion of residue expelled from the subglottis between all three subglottic landmarks. Specifically, the proportion of residue expelled was significantly higher when the deepest location of material was in the superior subglottic shelf compared to material in the inferior subglottic shelf ($p < .001$, mean difference = 0.37, $d = 0.53$) and trachea ($p < .001$, mean difference = 0.66, $d = 0.67$). Additionally, the proportion of residue expelled was significantly higher when the deepest location of material was in the inferior subglottic shelf compared to the trachea ($p = .002$, mean difference = 0.28, $d = 0.41$). An additional model including a two-way interaction between peak expiratory flow rate and aspiration location did not significantly improve model fit ($p = .549$, $LR = 1.22$, $f^2 = 0.03$).

Cough Expired Volume (First Cough)

Relationship Between Cough Airflow & Airway Clearance

No main effect of cough expired volume was shown in linear mixed models ($p = .073$, $f^2 = 0.06$). Cough expired volume significantly discriminated between ≥ 80% residue expelled ($p = .038$, $OR = 4.31$), but not between ≥ 25% residue expelled ($p = .225$, $OR = 4.81$).

Predictive Ability of Cough Expired Volume (First Cough)

A value of 1.30 L showed a high predicted probability of expelling ≥ 80% subglottic residue. The ROC analysis demonstrated suboptimal differentiation (AUC = 0.59) between "effective" and "ineffective" airway clearance with a binary classification of ≥ 80% residue expelled.

Cough Expired Volume (Entire Epoch)

Relationship Between Cough Airflow & Airway Clearance

Cough expired volume from the entire epoch demonstrated a significant linear relationship with the proportion of residue expelled from the subglottis ($p = .029$, $f^2 = 0.07$) while controlling for covariates (Table 2). However, CEV did not significantly discriminate between ≥ 80% residue expelled ($p = .062$, $OR = 2.16$).

Effect of Aspiration Location

Model comparisons showed that including aspiration location significantly improved model fit ($p < .001$, $LR = 33.94$). The full model showed a significant main effect of aspiration location ($p < .001$, $f^2 = 0.62$), whereas cough expired volume from the entire epoch was non-significant ($p = .569$, $f^2 = 0.005$). Pairwise comparisons showed significant differences in the proportion of residue expelled from the subglottis between all three subglottic landmarks. Specifically, the proportion of residue expelled from the subglottis was significantly higher when the deepest location of material was at the anterior commissure compared to material inferior ($p < .001$, mean difference = 0.72, $d = 1.43$) and superior ($p < .001$, mean difference = 0.39, $d = 0.79$) to the first ring of the cricoid cartilage. Additionally, the proportion of residue expelled was significantly higher when the deepest location of material was superior compared to inferior to the first ring of the cricoid cartilage ($p < .001$, mean difference = 0.32, $d = 0.65$). An additional model including a two-way interaction between cough expired volume from the entire epoch and aspiration location did not significantly improve model fit ($p = .186$, $LR = 3.37$, $f^2 = 0.07$).

Cough Volume Acceleration

Relationship Between Cough Airflow & Airway Clearance

Cough volume acceleration was not significantly associated with the proportion of residue expelled ($p = .057$, $f^2 = 0.07$). Furthermore, cough volume acceleration did not significantly discriminate between the proportion of residue expelled in binomial mixed models ($p > .05$).

<u>Penetration to the Vocal Folds</u>

Trial Characteristics

Bolus colorants included barium (60%), blue (23%), green (15%), and white (2%) dye. Bolus volumes included 90 mL (31%), 20 mL (5%), 10 mL (27%), 5 mL (13%), and patient-preferred (24%). Two trials (3.60%) demonstrated higher visual analog scale ratings after the cued cough and were assigned a rating of 0. Fifty-one percent of penetration events were entirely cleared from the vocal folds with a cued cough, 78% of coughs cleared at least 80% of penetration, and 91% of coughs cleared at least 50% of penetration. Fifty-eight percent of penetration events had residue on the left anterior $1/3^{rd}$ of the vocal folds, 56% on the right anterior $1/3^{rd}$, 42% on the left posterior $2/3^{rd}$, and 47% on the right posterior $2/3^{rd}$. Cough instructions included cues for a strong single cough (44%), a sequential cough (13%), both a strong and sequential cough (9%), or no qualifiers (35%). There were no significant differences in the proportion of penetration expelled between types of cough cues ($p > .05$). There was a moderate correlation between the amount of penetrant residue on the vocal folds before and after the cued cough ($r = 0.37$, $p = .004$, Appendix B).

Peak Expiratory Flow Rate, Cough Expired Volume (first cough), Cough Expired Volume (entire epoch), & Cough Volume Acceleration

No statistically significant relationship between peak expiratory flow rate (p = .320, f^2 = 0.02), cough expired volume from the first cough (p = .306, f^2 = 0.02), cough expired volume from the entire epoch (p = .379, f^2 = 0.02), or cough volume acceleration (p = .549, f^2 = 0.005) and the proportion of residue expelled from the vocal folds was found in linear mixed effects models.

Reliability

Intraclass correlation coefficients for inter-rater reliability were 0.83 for visual analog scale ratings of aspiration, 0.78 for penetration, 0.94 for peak expiratory flow rate, 0.73 for cough expired volume from the first cough, 0.91 for cough expired volume from the entire epoch, 0.77 for cough volume acceleration, and 0.70 for CrTot. Intraclass correlation coefficients for intra-rater reliability were 0.82 for aspiration, 0.89 for penetration, 0.96 for peak expiratory flow rate, 0.89 for cough expired volume from the first cough, 0.77 for cough expired volume from the entire epoch, 0.68 for cough volume acceleration, and 0.96 for CrTot.

Discussion

Voluntary cough is a central component of dysphagia management as it is commonly assessed during clinical swallowing evaluations, incorporated in screening protocols to identify dysphagia, and targeted in compensatory and rehabilitation dysphagia management plans. Though prior research has identified a close relationship between voluntary cough and swallowing dysfunction (Hegland et al., 2014; Pitts et al., 2008, 2010; Plowman et al., 2016), it remains unclear whether voluntary cough airflow is related to the ability to clear the airway of penetrant or aspirate material. Results from this retrospective investigation provide a first step towards establishing a clinically meaningful relationship between voluntary cough airflow and airway clearance. Our findings suggest that higher values of voluntary cough airflow, specifically peak expiratory flow rate and cough expired volume, are associated with a greater proportion of residue expelled from the subglottis. Additionally, the amount and depth of aspiration may play a role in this relationship, such that smaller amounts and more superior aspiration locations may require lower cough airflow. However, inadequate statistical power hindered our ability to confidently examine the role of this potential mediator in this relationship and the present findings should be interpreted within this context. Voluntary cough airflow was not associated with the ability to expel penetration from the vocal folds, potentially due to a large number of successful cough events. Collectively, these findings suggest that higher voluntary cough airflow is associated with improved airway clearance of aspiration.

Voluntary cough is commonly assessed during clinical swallowing evaluations and subjective judgments from clinicians have been a long-standing part of dysphagia clinical practice (Logemann, 1999). More recently, aerodynamic measures from gold-standard spirometric or handheld peak flow devices have garnered research and clinical interest to objectively quantify cough airflow during clinical swallowing evaluations (Watts et al., 2016). In fact, reduced voluntary cough airflow values have been found to predict airway invasion in Parkinson’s disease, stroke, and amyotrophic lateral sclerosis (Pitts et al., 2010; Plowman et al., 2016; Smith Hammond et al., 2001), which can be tested with low-cost analog or digital peak flow meters (Silverman et al., 2014). However, the predictive value of voluntary cough airflow as a metric for effectiveness of airway clearance has not been quantified. Results from the present study revealed that peak expiratory flow rate and cough expired volume (from the entire epoch) were significantly associated with effective airway clearance. We found that higher cough airflow values corresponded with a greater proportion of material expelled from the subglottis. More specifically, we identified clinically meaningful cut-offs for voluntary cough effectiveness, such that peak expiratory flow rate values of 3.23 L/s, 2.97 L/s, and 3.41 L/s differentiated between “effective” and “ineffective” airway clearance for ≥ 25%, ≥ 50%, and ≥ 80% subglottic residue expelled, respectively. These cut-offs complement prior research suggesting that peak expiratory flow rate values greater than 2.67 L/s predicted clearance of secretions and successful extubation in patients with neuromuscular disease (Bach & Saporito, 1996). Together, this may suggest that if a patient is able to generate sufficient airflow required for clearance of aspiration in the upper airway that this may also facilitate the removal of secretions. However, future research will be necessary to examine cough effectiveness in the context of both the upper and lower airways in a single patient population with validated secretion outcomes and gold-standard spirometric measurement of cough airflow.

The findings of this study, most specifically the clinically meaningful cut-offs, have important implications for the screening, assessment, and treatment of patients with dysphagia. These data suggest that voluntary cough peak flow can be used to assess both risk of airway invasion and risk of ineffective airway clearance. For example, a patient with Parkinson’s disease who demonstrates a voluntary cough peak flow value of 2.75 L/s during a clinical swallowing evaluation is at elevated risk for aspiration (e.g., based on Pitts et al., 2010 cut-off value of 5.24 L/s) and also at elevated risk for ineffective airway clearance. These two together indicate the possibility of both dysphagia and dystussia and would support the need for further objective swallowing and cough assessment. Additionally, objective peak flow values can be tracked over time to assess changes in cough effectiveness associated with disease progression or in response to treatment and whether these are associated with an elevated risk for ineffective airway clearance. Furthermore, these values can guide the development of treatment goals which are of high clinical significance for the rehabilitation of voluntary cough dysfunction. For example, in a patient with reduced cough effectiveness and known swallowing safety deficits, the goal for improved cough strength could be set to 5.30 L/s, which corresponds with more than 80% clearance of aspirate material.

Penetration to the level of the vocal folds is a frequent finding in individuals with dysphagia and associated with an increased risk of pneumonia (Ekberg & Nylander, 1982; Pikus et al., 2003). Thus, it is important to determine whether voluntary cough airflow values are associated with effective clearance of penetration. In the present study, the majority of cued coughs entirely cleared residue from the vocal folds, and we did not find a significant relationship between voluntary cough airflow and airway clearance. There are several potential explanations for these findings. Despite a wide range of cough airflow values, most coughs cleared penetration from the vocal folds which might suggest that higher cough expiratory airflow values are not necessary for airway clearance and that the majority of our participants met the requisite cough strength. This perspective complements prior research in a heterogenous cohort (traumatic brain injury, head and neck cancer, stroke) demonstrating that reflex coughs can effectively clear penetration from the airway (Wallace et al., 2020). Alternatively, our retrospective design may have introduced sampling bias (e.g., more frequently cueing less impaired patients to cough during penetration) prohibiting the ability to detect an effect of cough strength on clearance of penetrant. Regardless, future prospective investigations will be required to understand this potential relationship.

This work highlights the need to further investigate the role of voluntary cough effectiveness on airway clearance in patients with dysphagia. Given the retrospective, exploratory nature of this study and the lack of standardized instructions or cueing across participants, sampling and selection biases are potential confounds. Furthermore, cough airflow data were not captured simultaneously during FEES in this study. Therefore, these results suggest an associative relationship, rather than a causal relationship, between voluntary cough airflow obtained during spirometric cough testing and airway clearance visualized during cued voluntary coughs on FEES. Other demographic or cough-specific factors may contribute to one's ability to expel penetrant or aspirate from the airway, including age, height, number of coughs, lung volume at cough initiation, or temporal and kinematic respiratory parameters. An interaction between cough airflow and aspiration location (i.e., depth) may also play an important role, though the present study was underpowered to detect conventionally "small-to-moderate" effect sizes specific to aspiration depth. The amount of aspirate material present before a cued cough may also be a mediating factor in this relationship. It is also plausible that penetrant or aspirate material was inhaled further into the trachea during cued voluntary coughs, which we may not have been able to visualize on FEES. These will be important considerations for future well-controlled, prospective studies. It is important to note that cough airflow values (in particular peak expiratory airflow) may vary between spirometric equipment set-ups and peak flow meters. Therefore, future research will be necessary to determine cut-off values with low-cost tools that are easily implemented in clinical practice.

Conclusions

Voluntary cough dysfunction is highly prevalent across multiple patient populations and commonly used as a screening tool for swallowing safety deficits and potential target for compensatory and exercise-based dysphagia management. This preliminary, retrospective study supports the clinical utility of voluntary cough in dysphagia management given the findings of a relationship between voluntary cough airflow and clearance of aspiration from the subglottis in patients with neurodegenerative disease. Utilizing voluntary cough effectiveness cut-offs should be considered as a method to improve the identification of individuals at risk for swallowing safety airway clearance impairments. Additionally, these cut off values can be used to select specific clinically meaningful cough treatment targets. Lastly, these values enable researchers to ensure adequate statistical power to detect clinically meaningful change related to effective airway clearance.

Figure titles and legends

Figure 1: Examples of subglottic and vocal fold residue before and after cued coughs
Caption: PAS: penetration-aspiration scale

Figure 2: Inclusion and Exclusion Diagram
Caption: PAS: penetration-aspiration scale; FEES: flexible endoscopic evaluation of swallowing

Table 1: Participant demographics
Caption: PAS: penetration-aspiration scale; [1]One participant with spinocerebellar ataxia did not report disease duration from symptom onset. Therefore, standard deviation and range is not available.

Figure 3: The proportion of residue expelled across cough variables
Caption: PAS: penetration-aspiration scale; *Note*: Aspiration location categories refer to the deepest location of aspirate material before the cued cough

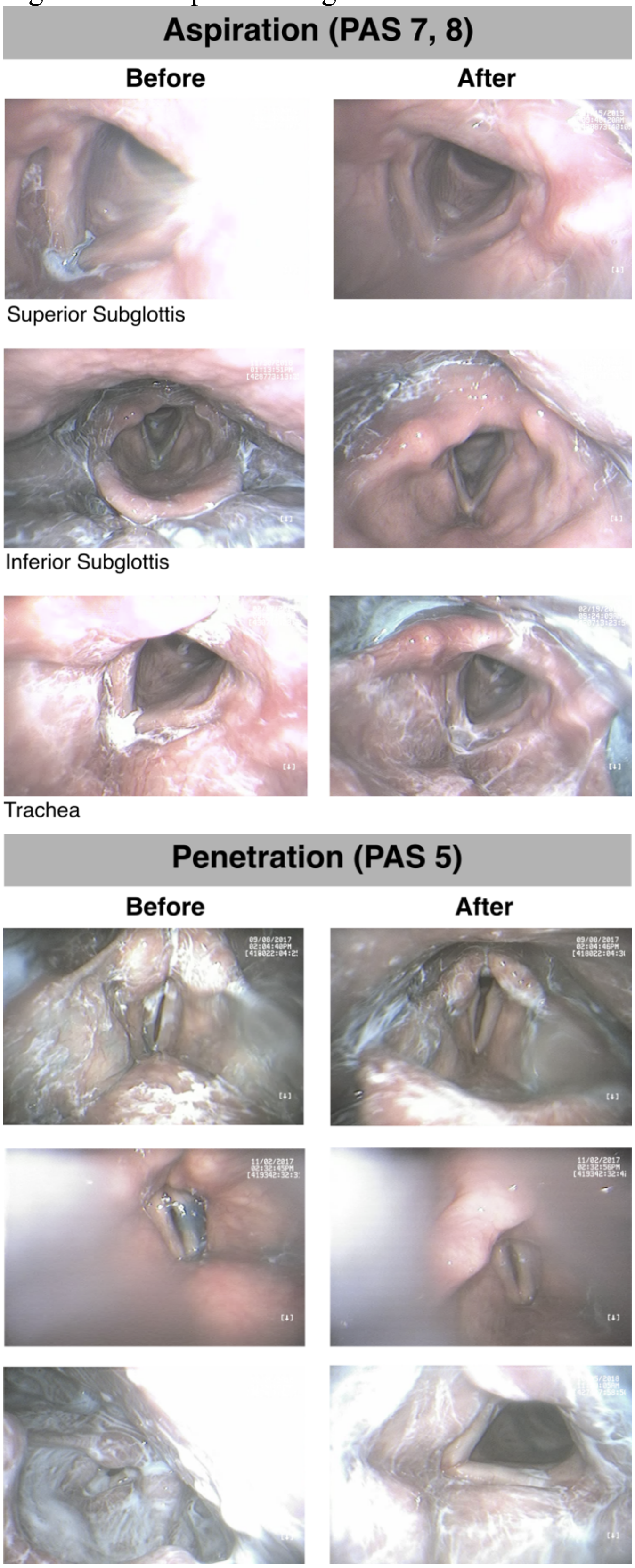
Table 2: Summary of Linear Mixed Effects Model Results

Table 3: Summary of Binomial Mixed Effects Model and Receiver Operating Characteristic Results
Caption: AUC: area under the curve; CI: confidence interval; ROC: Receiver operating characteristic

Figure 4: Probabilities of Cough Airflow Variables to Predict Aspiration Amount Expelled
Caption: Note: Predicted probabilities for statistically significant binomial mixed effects models are reported. These models account for additional covariates of sex, number of coughs during FEES, and number of coughs during spirometric voluntary cough testing.

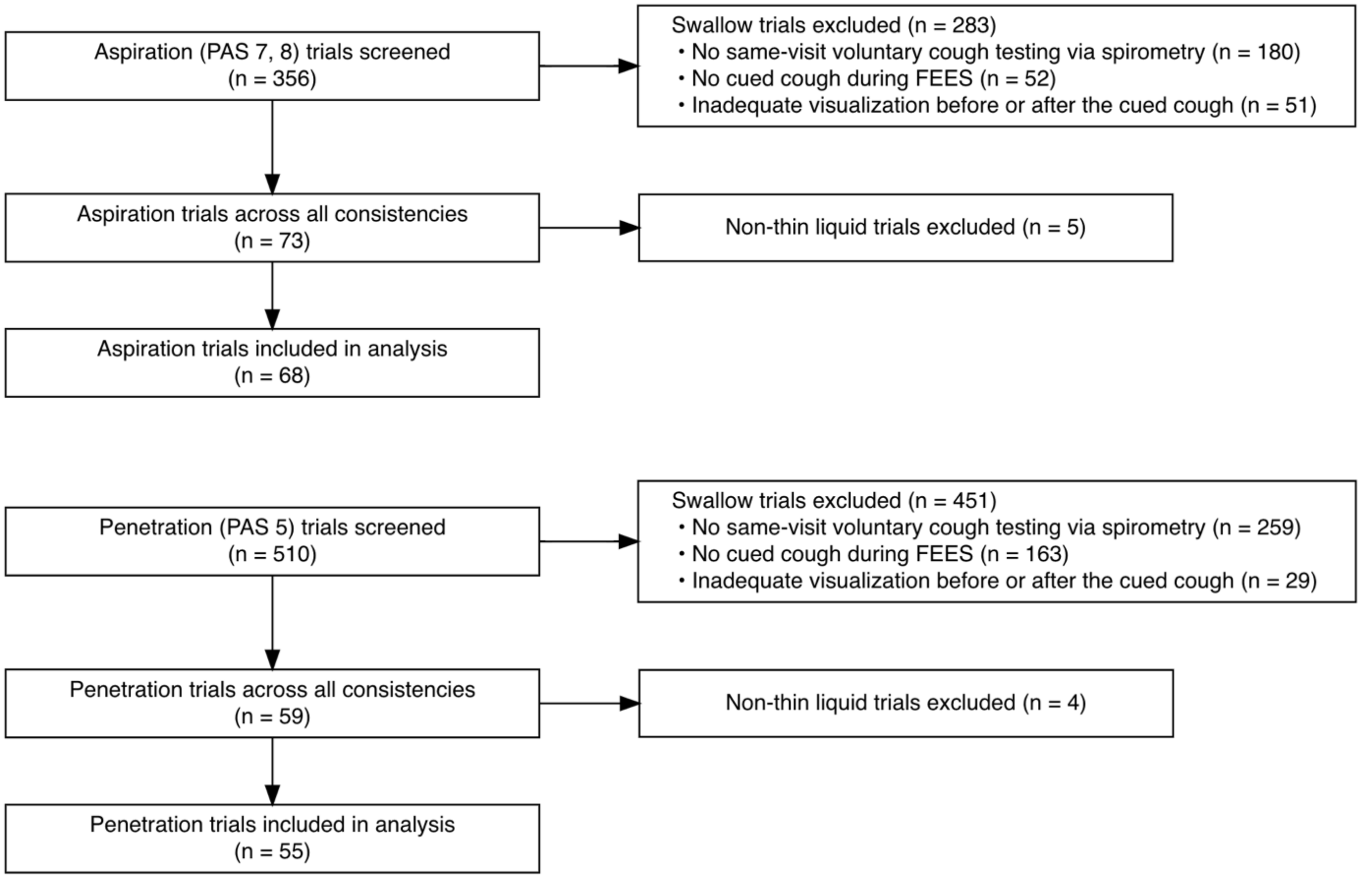
Figure 5: Sensitivity and Specificity of Cough Airflow Values to Predict Proportion of Aspiration Expelled
Caption: A: Peak expiratory flow rate (L/s) for ≥ 25% of aspiration expelled.
B: Peak expiratory flow rate (L/s) for ≥ 50% of aspiration expelled.
C: Peak expiratory flow rate (L/s) for ≥ 80% of aspiration expelled.
D: Cough expired volume from first cough (L) for ≥ 80% of aspiration expelled.
AUC: area under the curve. *Note*: Accuracy is provided for the cut-off value that maximizes sensitivity and specificity (shown in red). ROC analyses for cough airflow variables from statistically significant binomial models are shown.

Figure 1: Examples of subglottic and vocal fold residue before and after cued coughs



PAS: penetration-aspiration scale

Figure 2: Inclusion and Exclusion Diagram



PAS: penetration-aspiration scale; FEES: flexible endoscopic evaluation of swallowing

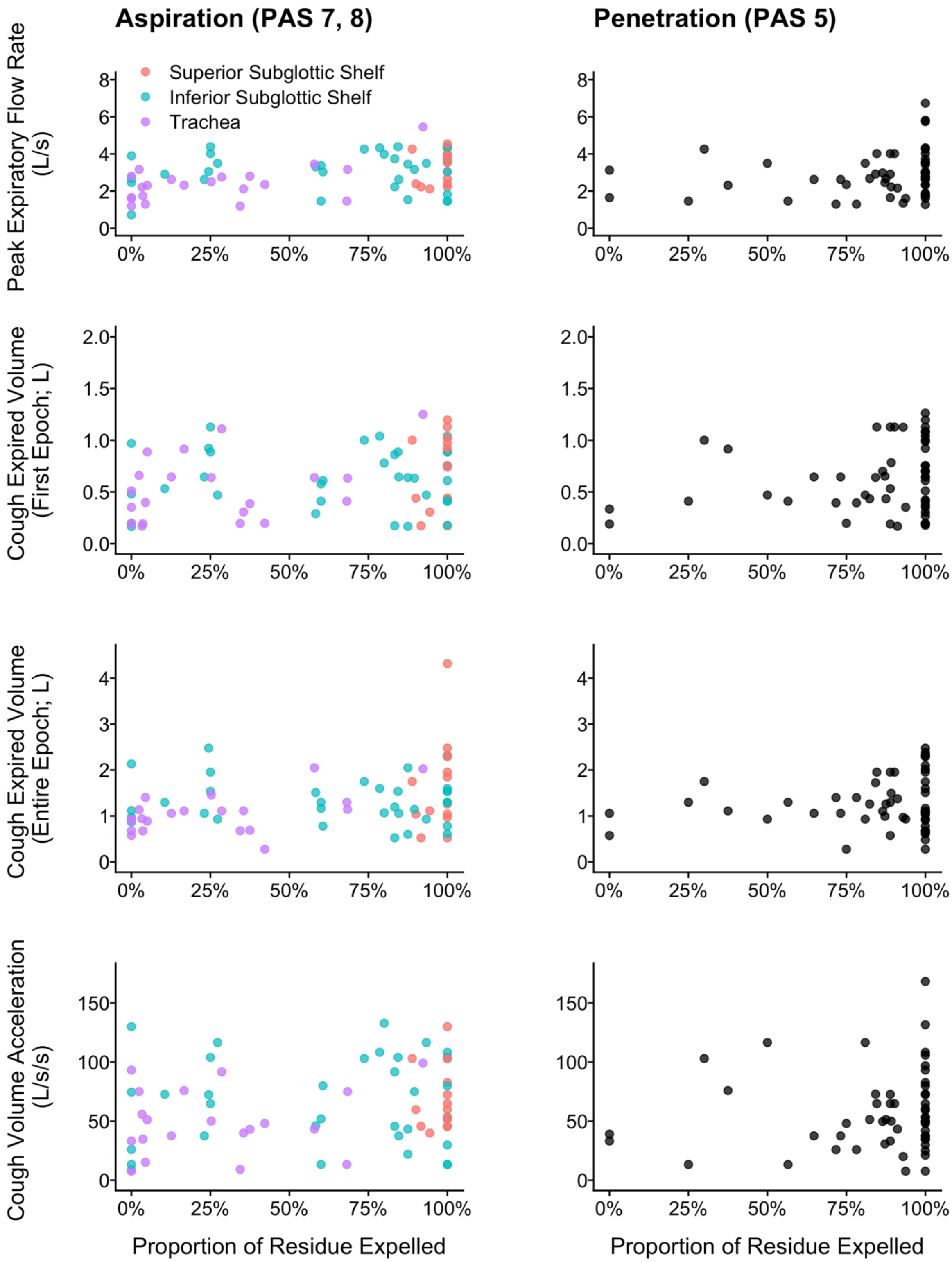
Table 1: Participant demographics

Aspiration Cohort	
Measures	*N* = 33 (68 trials)
Medical Diagnosis	
Parkinson's disease	26
Progressive supranuclear palsy	7
Sex	
Males	27
Females	6
Age (years)	
Mean ± standard deviation	70.10 ± 10.21
Range (minimum-maximum)	(56 – 89)
Disease Duration from Symptom Onset (years)	
Parkinson's Disease	
Mean ± standard deviation (range)	11.10 ± 6.34 (1.90 – 33.40)
Progressive supranuclear palsy	
Mean ± standard deviation (range)	7.21 ± 2.93 (3.05 – 10.90)
Penetration Cohort	
Measures	*N* = 30 (55 trials)
Medical Diagnosis	
Parkinson's disease	21
Progressive supranuclear palsy	5
Multiple systems atrophy – Cerebellar subtype	2
Spinocerebellar ataxia - Type 1	2
Sex	
Males	26
Females	4
Age (years)	

Mean ± standard deviation	68.96 ± 9.08
Range (minimum-maximum)	(41 – 82)
Disease Duration from Symptom Onset (years)	
Parkinson's Disease	
Mean ± standard deviation (range)	10.50 ± 5.39 (1.54 – 25.20)
Progressive supranuclear palsy	
Mean ± standard deviation (range)	5.05 ± 1.74 (3.05 – 6.62)
Multiple systems atrophy – Cerebellar subtype	
Mean ± standard deviation (range)	21 ± 25.20 (3.16 – 38.80)
Spinocerebellar ataxia - Type 1	
Mean[1]	10

PAS: penetration-aspiration scale
[1]One participant with spinocerebellar ataxia did not report disease duration from symptom onset. Therefore, standard deviation and range is not available.

Figure 3: The proportion of residue expelled across cough variables



PAS: penetration-aspiration scale; *Note*: Aspiration location categories refer to the deepest location of aspirate material before the cued cough.

Table 2: Summary of Linear Mixed Effects Model Results

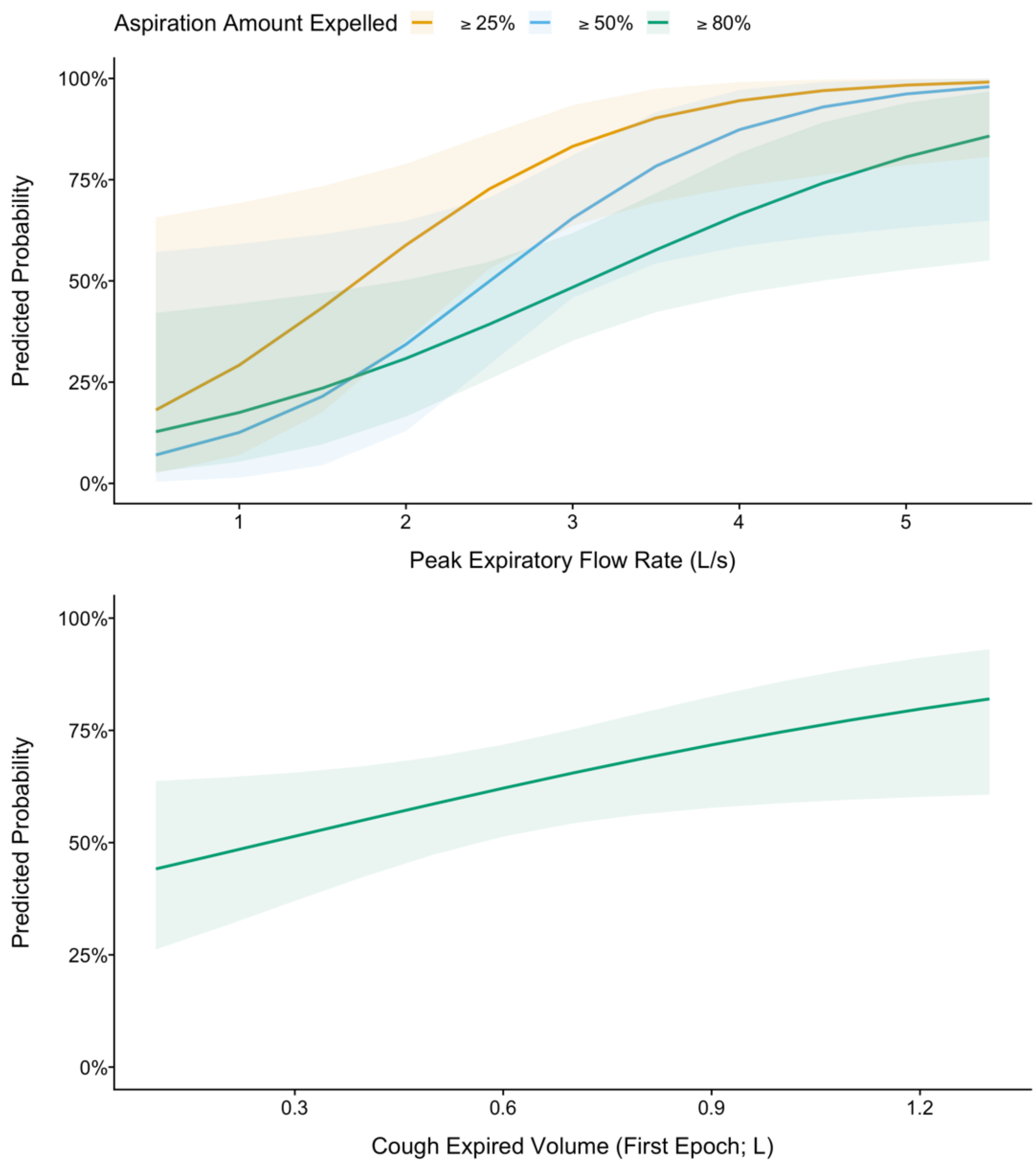
		Aspiration			Penetration		
Outcome	Predictor	β Coefficient	*p*-value	Variance Explained (f^2)	β Coefficient	*p*-value	Variance Explained (f^2)
Proportion of residue expelled	Peak expiratory flow rate	0.16	.004	17%	0.03	.320	2%
	Cough Expired Volume (First Cough)	0.32	.073	6%	0.12	.306	2%
	Cough Expired Volume (Entire Epoch)	0.17	.029	7%	0.06	.379	2%
	Cough Volume Acceleration	0.01	.057	7%	0.001	.549	0.5%

Table 3: Summary of Binomial Mixed Effects Model and Receiver Operating Characteristic Results

		Aspiration			
Outcome	Predictor	*p*-value	Odds Ratio	AUC (95% CI)	ROC Cut-Point
≥ 25% Residue Expelled	Peak expiratory flow rate	.018	3.47	0.73 (0.61, 0.85)	3.23 L/s
	Cough Expired Volume (First Cough)	.225	4.84	0.62 (0.47, 0.77)	0.40 L
	Cough Expired Volume (Entire Epoch)	.169	2.81	0.65 (0.50, 0.79)	1.14 L
	Cough Volume Acceleration	.155	1.02	0.64 (0.49, 0.80)	38.72 L/s/s
≥ 50% Residue Expelled	Peak expiratory flow rate	.033	3.63	0.70 (0.57, 0.83)	2.97 L/s
≥ 80% Residue Expelled	Peak expiratory flow rate	.015	2.10	0.66 (0.53, 0.79)	3.41 L/s
	Cough Expired Volume (First Cough)	.038	4.31	0.59 (0.45, 0.73)	0.70 L
	Cough Expired Volume (Entire Epoch)	.062	2.17	0.60 (0.46, 0.74)	1.52 L
	Cough Volume Acceleration	.092	1.01	0.62 (0.48, 0.75)	43.16 L/s/s
100% Residue Expelled	Peak expiratory flow rate	.056	1.80	0.64 (0.48, 0.80)	3.52 L/s

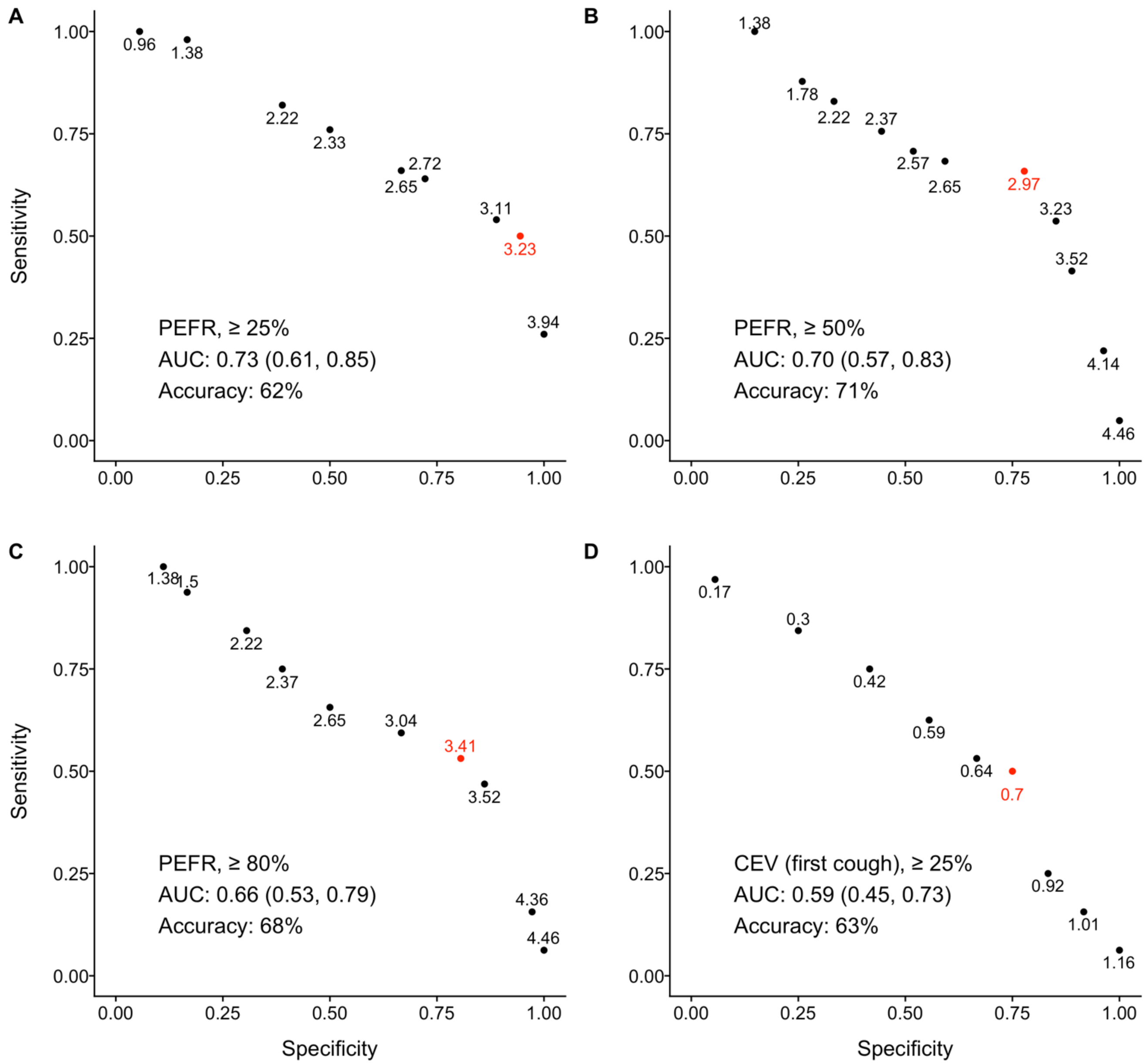
AUC: area under the curve; CI: confidence interval; ROC: Receiver operating characteristic

Figure 4: Probabilities of Cough Airflow Variables to Predict Aspiration Amount Expelled



Note: Predicted probabilities for statistically significant binomial mixed effects models are reported. These models account for additional covariates of sex, number of coughs during FEES, and number of coughs during spirometric voluntary cough testing.

Figure 5: Sensitivity and Specificity of Cough Airflow Values to Predict Proportion of Aspiration Expelled



A: Peak expiratory flow rate (L/s) for ≥ 25% of aspiration expelled.

B: Peak expiratory flow rate (L/s) for ≥ 50% of aspiration expelled.

C: Peak expiratory flow rate (L/s) for ≥ 80% of aspiration expelled.

D: Cough expired volume from first cough (L) for ≥ 80% of aspiration expelled.

AUC: area under the curve. *Note*: Accuracy is provided for the cut-off value that maximizes sensitivity and specificity (shown in red). ROC analyses for cough airflow variables from statistically significant binomial models are shown.

Appendix A: Sensitivity Power Analyses

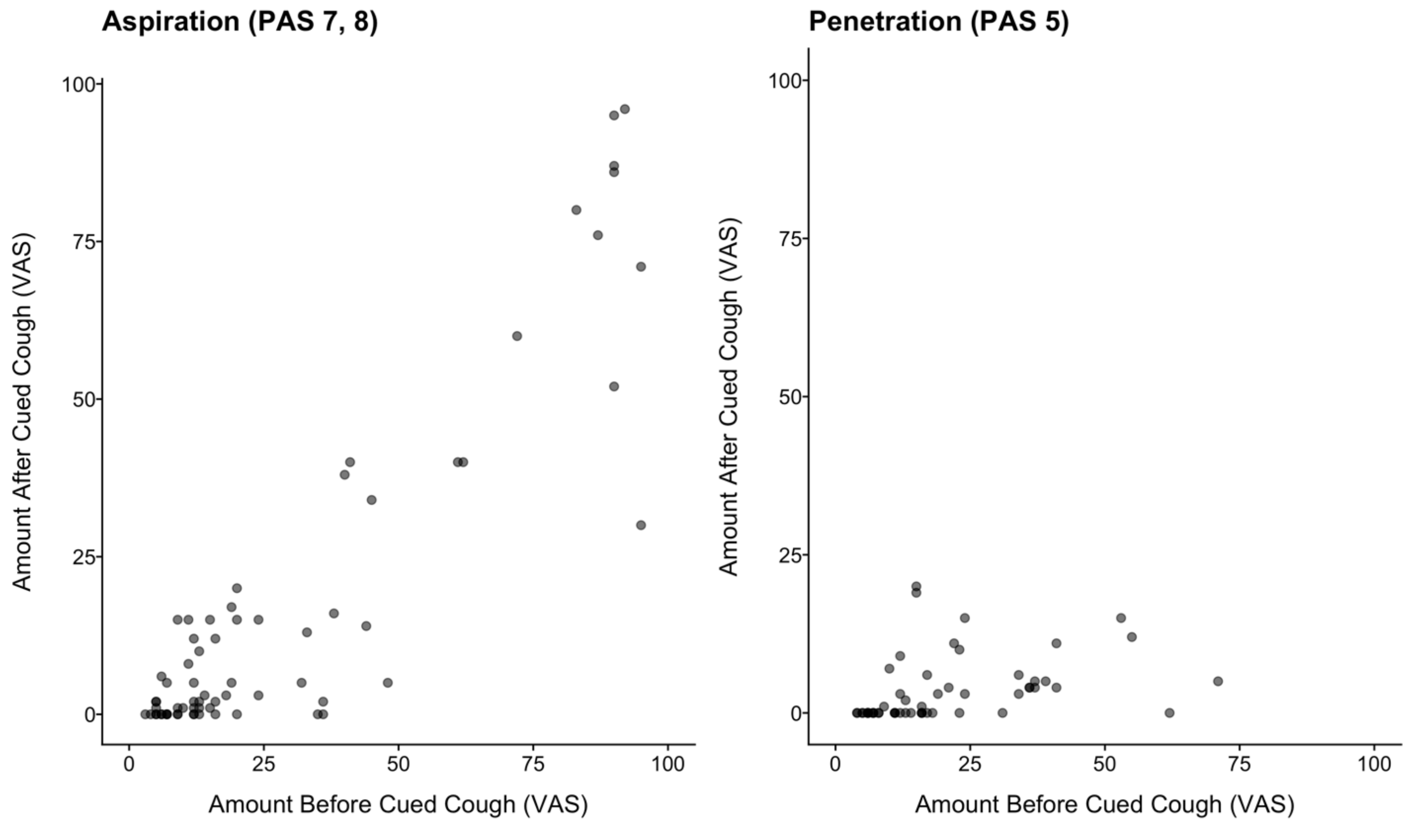
Aspiration Power Analyses		
Outcome	**Variable of Interest**	**Minimum Detectable Effect Size at 80% Power**
Proportion of Residue Expelled[1]	Peak Expiratory Flow Rate	$f^2 = 0.13$
	Cough Expired Volume (First Cough)	$f^2 = 0.13$
	Cough Expired Volume (Entire Epoch)	$f^2 = 0.10$
	Cough Volume Acceleration	$f^2 = 0.14$
	Main Effect of Aspiration Location in Peak Expiratory Flow Rate Model	$f^2 = 0.02$
	Interaction of Aspiration Location & Peak Expiratory Flow Rate	$f^2 = 0.78$
	Main Effect of Aspiration Location in Cough Expired Volume (Entire Epoch) Model	$f^2 = 0.03$
	Interaction of Aspiration Location & Cough Expired Volume (Entire Epoch)	$f^2 = 0.25$
≥ 25% Residue Expelled[2]	Peak Expiratory Flow Rate	$OR = 3.33$
	Cough Expired Volume (First Cough)	$OR = 1.05$
	Cough Volume Acceleration	$OR = 1.94$
≥ 50% Residue Expelled[2]	Peak Expiratory Flow Rate	$OR = 3.32$
	Peak Expiratory Flow Rate	$OR = 2.14$

≥ 80% Residue Expelled[2]	Cough Expired Volume (First Cough)	*OR* = 2.90
	Cough Expired Volume (Entire Epoch)	*OR* = 7.39
	Cough Volume Acceleration	*OR* = 1.04
100% Residue Expelled[2]	Peak Expiratory Flow Rate	*OR* = 2.23
Penetration Power Analyses		
Outcome	**Variable of Interest**	**Minimum Detectable Effect Size at 80% Power**
Proportion of Residue Expelled[1]	Peak Expiratory Flow Rate	$f^2 = 0.13$
	Cough Expired Volume (first cough)	$f^2 = 0.16$
	Cough Expired Volume (entire epoch)	$f^2 = 0.16$
	Cough Volume Acceleration	$f^2 = 0.17$

[1]Linear mixed effects model; [2]Binomial mixed effects model; *OR*: odds ratio

Note: All models include covariates of sex, number of coughs during flexible endoscopic evaluations of swallowing (FEES), and number of coughs during spirometric voluntary cough testing. Models with f^2 represent the amount of unique variance explained by the variable of interest, which was calculated from marginal pseudo-R^2. All penetration analyses and seven aspiration binomial mixed models (CEV from first epoch and CVA for ≥ 50 and 100% residue expelled, and CEV from entire epoch for ≥ 25%, ≥ 50%, and 100% residue expelled) were not reported due to failure of these models to converge.

Appendix B: Relationship between residue amount before and after a voluntary cued cough



PAS: penetration-aspiration scale; VAS: visual analog scale

Appendix C: Fixed and random effect estimates for linear and binomial mixed effects model

Aspiration Models								
Outcome	**Predictor**	**β Coefficient (Std. Error)**	**95% CI**	**Test statistic (*df*)**	***p*-value**	**Effect Size**	**Intercept Random Effect SD**	**Residual Random Effect SD**
Proportion of Residue Expelled	Intercept	0.13 (0.26)	-0.41 – 0.67	0.50 (32)	.618		0.17	0.33
	PEFR	0.16 (0.05)	0.05 – 0.26	3.09 (32)	.004	$f^2 = 0.17$		
	Sex	-0.01 (0.15)	-0.32 – 0.30	-0.07 (31)	.942	$d = -0.02$		
	CrTot FEES	-0.04 (0.03)	-0.10 – 0.02	-1.37 (32)	.181	$f^2 = 0.02$		
	CrTot Spirometry	0.04 (0.26)	-0.02 – 0.09	1.41 (32)	.167	$f^2 = 0.02$		
Proportion of Residue Expelled	Intercept	0.40 (0.25)	-0.12 – 0.91	1.57 (32)	.126		0.22	0.33
	CEV (first epoch)	0.32 (0.17)	-0.03 – 0.67	1.85 (32)	.073	$f^2 = 0.06$		
	Sex	-0.01 (0.16)	-0.35 – 0.33	-0.07 (31)	.948	$d = -0.02$		
	CrTot FEES	-0.05 (0.03)	-0.11 – 0.02	-1.40 (32)	.171	$f^2 = 0.03$		
	CrTot Spirometry	0.04 (0.03)	-0.02 – 0.09	1.45 (32)	.157	$f^2 = 0.03$		
Proportion of Residue Expelled	Intercept	0.53 (0.22)	0.08 – 0.97	2.41 (32)	.022		0.21	0.32
	CEV (entire epoch)	0.17 (0.08)	0.02 – 0.32	2.28 (32)	.029	$f^2 = 0.07$		
	Sex	-0.08 (0.16)	-0.41 – 0.26	-0.46 (31)	.647	$d = -0.12$		
	CrTot FEES	-0.05 (0.03)	-0.11 – 0.02	-1.56 (32)	.129	$f^2 = 0.03$		
	CrTot Spirometry	0.02 (0.03)	-0.04 – 0.07	0.65 (32)	.520	$f^2 = 0.002$		
	Intercept	0.34 (0.24)	-0.15 – 0.83	1.40 (32)	.172		0.20	0.33

Proportion of Residue Expelled	CVA	0.01 (0.001)	-0.001 – 0.007	1.97 (32)	.057	$f^2 = 0.07$		
	Sex	-0.09 (0.16)	-0.41 – 0.23	-0.56 (31)	.576	*d* = -0.14		
	CrTot FEES	-0.06 (0.03)	-0.12 – 0.004	-1.90 (32)	.067	$f^2 = 0.04$		
	CrTot Spirometry	0.08 (0.03)	0.02 – 0.15	2.66 (32)	.012	$f^2 = 0.11$		
≥ 25% Residue Expelled	Intercept	-2.10 (2.05)	0. – 0.93	-1.02	.307		1.04	1.81
	PEFR	1.24 (0.53)	0.22 – 2.27	2.37	.018	*OR* = 3.47		
	Sex	0.23 (1.18)	-2.12 – 2.53	0.19	.847	*OR* = 1.25		
	CrTot FEES	-0.21 (0.24)	-0.67 – 0.26	-0.87	.386	*OR* = 0.81		
	CrTot Spirometry	0.14 (0.23)	-0.31 – 0.59	0.61	.542	*OR* = 1.15		
≥ 25% Residue Expelled	Intercept	0.84 (1.79)	-2.66 – 4.34	0.47	.639		1.20	1.81
	CEV (first epoch)	1.58 (1.30)	-0.97 – 4.12	1.21	.225	*OR* = 4.84		
	Sex	0.11 (1.19)	-2.21 – 2.44	0.09	.929	*OR* = 1.11		
	CrTot FEES	-0.15 (0.26)	-0.65 – 0.36	-0.57	.568	*OR* = 0.86		
	CrTot Spirometry	-0.001 (0.20)	-0.39 – 0.39	-0.005	.996	*OR* = 1.00		
≥ 25% Residue Expelled	Intercept	1.27 (1.60)	-1.89 – 4.46	0.79	.431			
	CEV (entire epoch)	1.03 (0.75)	-0.43 – 2.50	1.38	.169	*OR* = 2.81		
	Sex	-0.24 (1.19)	-2.53 – 2.08	-0.21	.837	*OR* = 0.78		
	CrTot FEES	-0.16 (0.25)	-0.65 – 0.34	-0.65	.519	*OR* = 0.85		
	CrTot Spirometry	-0.12 (0.19)	-0.49 – 0.27	-0.59	.558	*OR* = 0.89		
≥ 25% Residue Expelled	Intercept	0.003 (1.78)	-3.51 – 3.50	0.002	.999		1.29	1.81
	CVA	0.02 (0.01)	-0.01 – 0.05	1.42	.155	*OR* = 1.02		
	Sex	-0.03 (1.23)	-2.41 – 2.38	-0.03	.980	*OR* = 0.97		

	CrTot FEES	-0.26 (0.26)	-0.78 – 0.26	-0.98	.329	*OR* = 0.77		
	CrTot Spirometry	0.29 (0.28)	-0.26 – 0.84	1.05	.295	*OR* = 1.34		
≥ 50% Residue Expelled	Intercept	-2.79 (2.34)	0 – 1.79	-1.19	.233		1.23	1.81
	PEFR	1.29 (0.60)	0.10 – 2.47	2.14	.033	*OR* = 3.63		
	Sex	-0.90 (1.27)	-3.50 – 1.58	-0.71	.478	*OR* = 0.41		
	CrTot FEES	-0.21 (0.25)	-0.69 – 0.27	-0.86	.391	*OR* = 0.81		
	CrTot Spirometry	0.30 (0.26)	-0.21 – 0.81	1.16	.248	*OR* = 1.35		
≥ 80% Residue Expelled	Intercept	-2.26 (1.51)	-4.61 – 0.69	-1.50	.133		0.13	1.81
	PEFR	0.74 (0.31)	0.14 – 1.35	2.43	.015	*OR* = 2.10		
	Sex	0.02 (0.82)	-1.61 – 1.64	0.98	.978	*OR* = 1.02		
	CrTot FEES	-0.29 (0.22)	-0.73 – 0.14	0.18	.183	*OR* = 0.75		
	CrTot Spirometry	0.27 (0.18)	-0.08 – 0.62	0.13	.133	*OR* = 1.31		
≥ 80% Residue Expelled	Intercept	0.11 (0.92)	-1.71 – 1.91	0.12	.907		0.47	1.81
	CEV (first epoch)	1.46 (0.70)	0.09 – 2.84	2.08	.038	*OR* = 4.31		
	Sex	-0.49 (0.70)	-1.84 – 0.88	-0.70	.487	*OR* = 0.62		
	CrTot FEES	-0.23 (0.14)	-0.51 – 0.04	-1.67	.095	*OR* = 0.79		
	CrTot Spirometry	0.20 (0.12)	-0.04 – 0.43	1.65	.100	*OR* = 1.22		
≥ 80% Residue Expelled	Intercept	0.51 (0.87)	-1.20 – 2.20	0.58	.560		0.54	1.81
	CEV (entire epoch)	0.77 (0.42)	-0.04 – 1.59	1.87	.062	*OR* = 2.17		
	Sex	-0.72 (0.71)	-2.12 – 0.67	-1.01	.312	*OR* = 0.49		
	CrTot FEES	-0.23 (0.14)	-0.49 – 0.04	-1.70	.090	*OR* = 0.79		
	CrTot Spirometry	0.12 (0.12)	-0.12 – 0.36	1.01	.315	*OR* = 1.13		

≥ 80% Residue Expelled	Intercept	0.33 (0.93)	-1.47 – 2.15	0.36	.721		0.52	1.81
	CVA	0.01 (0.007)	0 – 0.03	1.68	.092	*OR* = 1.01		
	Sex	-0.76 (0.70)	-2.12 – 0.62	-1.08	.282	*OR* = 0.47		
	CrTot FEES	-0.31 (0.15)	-.60 – -0.01	-2.01	.045	*OR* = 0.74		
	CrTot Spirometry	0.31 (0.14)	0.03 – 0.59	2.17	.030	*OR* = 1.36		
100% Residue Expelled	Intercept	-3.44 (1.84)	0 – 0.16	-1.87	.061		0.05	1.81
	PEFR	0.59 (0.31)	-0.01 – 1.19	1.91	.056	*OR* = 1.80		
	Sex	0.42 (1.01)	-1.56 – 2.41	0.42	.677	*OR* = 1.52		
	CrTot FEES	-0.32 (0.23)	-0.78 – 0.13	-1.38	.169	*OR* = 0.73		
	CrTot Spirometry	0.36 (0.18)	0.01 – 0.71	2.03	.043	*OR* = 1.43		
Penetration Models								
Outcome	**Predictor**	**β Coefficient (Std. Error)**	**95% CI**	**Test statistic (*df*)**	***p*-value**	**Effect Size**	**Intercept Random Effect SD**	**Residuals Random Effect SD**
Proportion of Residue Expelled	Intercept	0.88 (0.14)	0.59 – 1.18	6.11 (28)	< .0001		0.08	0.24
	PEFR	0.03 (0.03)	-0.03 – 0.10	1.02 (22)	.320	f^2 = 0.02		
	Sex	-0.13 (0.12)	-0.37 – 0.10	-1.16 (28)	.256	*d* = 0.08		
	CrTot FEES	-0.002 (0.02)	-0.04 – 0.04	-0.15 (22)	.882	f^2 = 0.001		
	CrTot Spirometry	0.001 (0.02)	-0.04 – 0.04	0.03 (22)	.975	f^2 = 0.001		
Proportion of Residue Expelled	Intercept	0.87 (0.13)	0.60 – 1.14	6.52 (28)	< .0001		0.05	0.24
	CEV (first epoch)	0.12 (0.11)	-0.11 – 0.34	1.05 (22)	.306	f^2 = 0.02		
	Sex	-0.16 (0.11)	-0.38 – 0.07	-1.44 (28)	.162	*d* = -0.33		
	CrTot FEES	-0.01 (0.02)	-0.05 – 0.03	-0.49 (22)	.629	f^2 = 0.001		

	CrTot Spirometry	0.02 (0.02)	-0.02 – 0.06	1.07 (22)	.296	$f^2 = 0.001$		
Proportion of Residue Expelled	Intercept	0.89 (0.12)	0.64 – 1.14	7.29 (28)	< .0001		0.04	0.24
	CEV (entire epoch)	0.06 (0.07)	-0.08 – 0.19	9.00 (22)	.379	$f^2 = 0.02$		
	Sex	-0.18 (0.11)	-0.39 – 0.04	-1.68 (28)	.104	$d = -0.36$		
	CrTot FEES	-0.01 (0.02)	-0.05 – 0.03	-0.33 (22)	.746	$f^2 = 0.001$		
	CrTot Spirometry	0.02 (0.02)	-0.03 – 0.06	0.79 (22)	.435	$f^2 = 0.001$		
Proportion of Residue Expelled	Intercept	0.93 (0.13)	0.66 – 1.19	7.17 (28)	< .0001		0.08	0.24
	CVA	0.001 (0.01)	-0.01 – 0.01	0.61 (22)	.549	$f^2 = 0.005$		
	Sex	-0.16 (0.11)	-0.39 – 0.07	-1.42 (28)	.167	$d = -0.33$		
	CrTot FEES	-0.009 (0.02)	-0.05 – 0.03	-0.45 (22)	.660	$f^2 = 0.001$		
	CrTot Spirometry	0.02 (0.02)	-0.03 – 0.06	0.72 (22)	.479	$f^2 = 0.01$		

CI: confidence interval; df: degrees of freedom; SD: standard deviation; CrTot: number of coughs; PEFR: peak expiratory flow rate; CEV: cough expired volume; CVA: cough volume acceleration

Note: Sex reference level is female.

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