Heterogenous Treatment Effects Following Inspiratory Muscle Training during Recovery from Post-Acute COVID-19 Syndrome

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ABSTRACT

Purpose: To investigate whether heterogeneous treatment effects occur for changes in inspiratory muscle strength, perceived dyspnoea, and health-related quality of life (QoL), following eight-weeks unsupervised home-based inspiratory muscle training (IMT) in adults with post-acute COVID-19 syndrome. **Methods**: In total, 147 adults with self-reported prior COVID-19 either completed an eight-week home-based IMT intervention (*n*=111; 92 females; 48±11 years; 9.3±3.6 months post-acute COVID-19 infection) or acted as "usual care" wait list controls (*n*=36; 34 females; 49±12 years; 9.4±3.2 months post-acute COVID-19 infection). **Results:** Applying a Bayesian framework, we found clear evidence of heterogeneity of treatment response for inspiratory muscle strength: the estimated difference between standard deviations (SDs) of the IMT and control groups was 22.8 cmH_2O (75% Credible Interval (CrI): 4.7-37.7) for changes in maximal inspiratory pressure (MIP), and 86.8 pressure time-units (PTUs; 75% CrI: 55.7-116.7) for sustained MIP (SMIP). Conversely, there were minimal differences in the SDs between the IMT and the control group for changes in perceived dyspnoea and health-related QoL, providing no evidence of heterogeneous treatment effects. Higher cumulative power during the IMT intervention was related to changes in MIP (*ß*=10.9 [95% CrI: 5.3-16.8] cmH_2O per 1SD) and SMIP (*ß*=63.7 [32.2-95.3] PTUs per 1SD), clearly indicating an IMT dose response for changes in inspiratory muscle strength. Older age (>50 years), a longer time post-acute COVID-19 (>3 months), and greater severity of dyspnoea at baseline were also associated with smaller improvements in inspiratory muscle strength. **Conclusion:** Heterogenous individual responses occurred following an eight-week home-based IMT programme in people with post-acute COVID-19 syndrome. Consistent with standard exercise theory, larger improvements in inspiratory muscle strength are strongly related to a greater cumulative dose of IMT.

Keywords: post-acute COVID-19 syndrome, long COVID, rehabilitation, treatment, breathlessness, breathing

INTRODUCTION

Post-acute Coronavirus Disease19 (COVID-19) syndrome (1), often referred to as long COVID, is estimated to affect 1 in 10 individuals with COVID-19, which in the UK, equates to ~2.3 million people as of October 6th 2022 (2). Whilst the symptoms of post-acute COVID-19 syndrome are diverse and vary between individuals, breathlessness is amongst the most common and debilitating (3). Given the prevalence and burden of post-acute COVID-19 syndrome, there is a need to develop feasible and effective rehabilitation strategies, emphasised by recent evidence that prior vaccination only partially protects against developing post-acute COVID-19 syndrome (4).

There are currently limited rehabilitation strategies available for people with post-acute COVID-19 syndrome, but a recent randomised controlled trial demonstrated that inspiratory muscle training (IMT) is an effective intervention to enhance recovery from COVID-19 (5). IMT involves repeated inspiratory breaths performed using a resisted air-flow device and is designed to challenge and elicit adaptations in the respiratory musculature (6). Following eight weeks of unsupervised home-based IMT, there were mean improvements in perceived dyspnoea, inspiratory muscle strength, device-measured moderate-intensity physical activity, and estimated aerobic fitness (5). IMT is low cost and simple to deliver remotely, making it ideal to integrate as part of a multi-component rehabilitation programme for people with post-acute COVID-19 syndrome.

The efficacy of a treatment, including exercise interventions, is typically presented as a mean change compared to a control group, yet this approach may overlook potentially important individual differences in the response to the intervention, which are referred to as ‘heterogenous treatment effects’ (7). Quantifying and predicting such inter-individual variation is the basis of precision medicine, which aims to prescribe individually tailored

interventions to optimise treatment outcomes (8,9). Nevertheless, whether meaningful individual variation in response to either supervised or unsupervised exercise training truly exists is somewhat contentious; many previous studies have not applied statistical frameworks that account for technical, biological, and random error (10,11). Specifically, to be able to conclude that true individual differences in the response to the intervention exist, there must be evidence of larger variation in the change scores in the intervention group compared to the change scores from an appropriate time-matched control group (10). If this is the case, it would be appropriate to subsequently explore moderating factors that may explain the additional variation in response in the intervention group (10). Conversely, if the variation of change is similar between the intervention and the control groups, then it is not possible to conclude that there were any individual responses caused by the intervention *per se* (10). Whilst there may still be a mean intervention effect, and large variation around the mean change in the intervention group, it could only be concluded that this was caused by factors present in both the intervention and control groups (i.e., technical, biological, or random error; (10)).

Any variation in treatment effects may be more likely to be present and/or be more pronounced in studies of the real-world effectiveness of interventions, particularly involving home-based exercise, where the lack of supervision could result in large differences in individual adherence to the prescribed intervention (i.e. intervention fidelity) (12). Furthermore, the diverse presentation of post-acute COVID-19 syndrome (3,13) may lead to large inter-individual treatment effects. Thus, the primary aim of this study was to investigate whether heterogeneous treatment effects occur following eight weeks of unsupervised IMT in adults with post-acute COVID-19 syndrome. Where heterogenous treatment effects were identified, two secondary aims were to: *1)* quantify the proportion of individuals expected to make an improvement following IMT; and *2)* perform sub-analyses on participant

characteristics and IMT dose-related variables to explore relative treatment effect modification.

METHODS

Participants

The sample for this study is from an eight-week, single-centre, two-arm randomised controlled trial (RCT) which investigated the effect of home-based IMT on inspiratory muscle function, self-reported health status, and physical activity levels, in adults with self-reported post-acute COVID-19 syndrome (5). The mean intervention effects are presented in McNarry *et al.* (5). For this secondary analysis of potential heterogeneous treatment effects, of 281 participants originally randomised, we excluded all participants who did not complete the study and/or had incomplete outcome data (*n*=134). This resulted in a sample of 147 participants who were randomised to either the IMT (*n*=111) or a "usual care" wait list control (*n*=36) group (**Table 1**). All participants provided informed consent following approval by the NHS Research Ethics Committees (Ref: 20/HRA/3536). The study was pre-registered on the Health and Care Research Wales Research Directory (Ref: 48075) and conducted in accordance with the Declaration of Helsinki.

Outcomes

Inspiratory muscle strength was measured at baseline and post-intervention using a handheld inspiratory resistive flow device (PrO_2^{TM}, PrO_2Fit Health Incorporated, RI, USA). Following familiarisation with the device, participants performed full expiration to residual volume, followed by a maximal sustained inspiratory effort to measure both maximal inspiratory pressure (MIP) and sustained maximal inspiratory pressure (SMIP). The assessment was performed at home and supervised via remote teleconference (due to lockdown) with strong verbal encouragement provided. Both MIP and SMIP are important clinical markers of respiratory function (14), which the PrO_2^{TM} device measures with high reliability (15).

Changes in dyspnoea were assessed using the Transition Dyspnoea Index (TDI; (16)) and the 15-item King's Brief Interstitial Lung Disease (KBILD) Questionnaire (17). The TDI is a clinically validated questionnaire, which measures changes in dyspnoea from baseline using the Baseline Dyspnoea Index (BDI) in three domains (functional impairment, magnitude of task, and magnitude of effort), and was completed post-intervention only. The KBILD was completed at baseline and post-intervention and provides a score for overall health-related quality of life from responses within three sub-categories (Psychological, Breathlessness and Activities, and Chest Symptoms).

IMT Intervention

Participants randomised to the IMT group were prescribed an eight-week home-based IMT intervention, with a frequency of three sessions per week performed on non-consecutive days. IMT training was delivered using the same PrO_2^{TM} device that was used for assessing MIP and SMIP. Training in the use of the PrO_2^{TM} device was provided to each participant during a one-to-one video conferencing meeting.

Each IMT session lasted ~20 minutes. Participants were prescribed a maximum of six blocks of six inspirations, with each breath interspersed with a short period of resting recovery which progressively decreased from 40 seconds to 10 seconds within each distinct block. Each inspiratory breath was performed at >80% of SMIP ascertained from a maximal inspiratory effort, performed prior to each IMT session to allow for both training progression, as well as potential day-to-day fluctuations in respiratory function due to the relapsing/remitting nature of post-acute COVID-19 syndrome (3). Each inspiration was performed for as long as possible and, during each IMT session, participants completed as many inspirations as they could prior to failure, defined as not achieving 80% SMIP on three consecutive breaths.

The PrO_2^{TM} device synchronises wirelessly to a computer, smartphone or tablet via an application (https://apps.apple.com/us/app/pro2-fit/id1321623265), which provided real-time graphic biofeedback during each session. This also facilitated remote recording and cloud storage of the characteristics of all participants' training sessions. The following characteristics of the IMT training sessions were subsequently extracted: *(1)* total completed sessions; *(2)* mean training frequency (sessions/week over eight weeks); *(3)* total breaths; *(4)* mean number of breaths per session; *(5)* mean breath duration; and *(6)* total cumulative power across the intervention. As total cumulative power across the intervention could be influenced by baseline MIP and/or SMIP, this was expressed in both absolute terms and relative to baseline MIP and SMIP in the analysis. The variation in IMT training characteristics is shown in **Table 2.**

Statistical Analysis

All analyses were conducted within a Bayesian framework and are reported in accordance with the CHAMP statement (18). Seven dependent variables were selected, including the TDI, KBILD and its sub-categories, and MIP and SMIP. Individual change scores were calculated by subtracting baseline from post-intervention values (except for the TDI where the post-intervention score reflects change from baseline). Variation in change scores were compared across the intervention and control group with greater standard deviations for the intervention group taken as evidence of heterogeneous treatment effects. Distributional models estimating mean and variance parameters were fitted for each dependent variable, either including group as a predictor for the standard deviation (M_2), or not (M_1). Bayes factors $\left(\frac{p(y|M_1)}{p(y|M_2)}\right)$ were calculated with the strength of evidence in favour of M_1 (no heterogeneous treatment effects) or M_2 (heterogeneous treatment effects) assessed according to a previously defined scale (19). The data-generating model for each variable was assessed

by fitting normal, skew normal, and *t*-distributions with the most appropriate distribution type for each outcome determined using the Watanabe-Akaike information criterion. Model checking and selection was performed to increase the precision of results. Differences in standard deviation between the intervention and control were estimated using posterior predictions and 95% credible intervals (CrIs).

Where strong evidence of heterogenous treatment effects was obtained (Bayes factor >10), proportion of response and factors associated with relative treatment effect modification were explored. Proportion of response was estimated by subtracting the mean difference between groups and the difference in the standard deviations to calculate the intervention-response standard deviation and calculating the proportion of the distribution exceeding zero (20). Subgroups comprising binary classification of patient characteristics (time since COVID [low: ≤ 3 months; high: >3 months], Body Mass Index (BMI) [low: <25 $kg•m^{-2}$; high: ≥25 $kg•m^{-2}$], age [low: <50 years; high: ≥50 years], baseline KBILD total score [low: <53; high: ≥53], and baseline BDI [low: ≤6 units; high: >6 units]) were created and the difference in mean treatment-effect estimated, with Bayes factors and 95% CrIs calculated to interpret relative treatment-effect modification. For age, baseline KBILD and baseline BDI score, low and high scores were split based on the median, whilst for BMI the standard overweight cut-off of 25 $kg•m^{-2}$ was applied and for time since COVID a 3-month cut-off was applied based on the World Health Organisation clinical case definition of long COVID (21). For IMT-related variables, relative treatment effect modification was assessed by linearly regressing change scores on each variable standardised by dividing by the sample standard deviation. Default weakly informative Student-*t* prior and half-*t* priors with three degrees of freedom were used for intercept and variance parameters (22). All analyses were performed using the R wrapper package brms interfaced with Stan to perform sampling (23) and the R package

bridge sampling to calculate Bayes factors. Convergence of parameter estimates was obtained for all models with Gelman-Rubin R-hat values below 1.1 (24).

Results

KBILD and TDI

The best model fit for KBILD sub-domain and total score, and the TDI score, was obtained using a normal distribution. There were minimal differences in the standard deviation scores between the IMT and the control group for all KBILD sub-domains (**Figure 1**), the KBILD total score (**Figure 1**), and the TDI score (**Figure 2**), and in all cases the Bayes factor was <3, providing no evidence of individual responses to IMT (**Table 3**).

MIP and SMIP

The best model fit for MIP was a *t*-distribution and for SMIP it was a normal distribution. The estimated difference in standard deviations of the IMT and the control group was 22.8 cmH_2O (75% CrI: 4.7-37.7) for MIP, and 86.8 pressure time-units (75% CrI: 55.7-116.7) for SMIP. In both cases, the Bayes factor was >100, providing extreme evidence of individual responses to IMT (**Figure 3**, **Table 3**). The estimated proportion of response was 0.84 (95% CrI: 0.63-1.0) for MIP and 0.95 (95% CrI: 0.76-1.0) for SMIP (**Table 3**).

There was evidence of an IMT dose-response: a greater treatment effect for both MIP and SMIP was shown with a higher number of IMT sessions (moderate evidence for both), more breaths performed per session (extreme evidence for MIP, very strong evidence for SMIP), a larger number of total breaths performed over the intervention (very strong evidence for both), a higher mean breath duration (strong evidence for MIP, very strong evidence for SMIP), a higher total cumulative power expressed absolutely or relative to baseline MIP/SMIP (all extreme evidence) (**Table 4**).

Several participant characteristics also appeared to alter the treatment effect: the change in both MIP and SMIP was greater in younger participants (extreme evidence for MIP, strong

evidence for SMIP), those with COVID-19 less than 3 months before baseline assessment (strong evidence for both), and those who had less severe dyspnoea at baseline (extreme evidence for MIP, strong evidence for SMIP; **Figure 4**). There was less evidence that treatment effect was altered by baseline BMI (anecdotal evidence favouring no effect for MIP, moderate evidence for an effect for SMIP) or baseline KBILD total score (moderate evidence for both; **Figure 4**). Point estimates from standard Pearson correlations identified limited, but likely non-zero associations between age, baseline dyspnoea (BDI score) or time since COVID-19 infection and any IMT dose variable (r<0.3).

DISCUSSION

This study investigated whether heterogeneity of treatment effects occurs following eight weeks of unsupervised home-based IMT in adults recovering from COVID-19. There were three key findings: *1)* there were clear heterogeneous treatment effects for changes in respiratory muscle strength, and consistent with standard exercise theory, larger improvements were related to a greater accumulated dose of IMT (more sessions, more breaths, greater cumulative power etc.); *2)* improvements in respiratory muscle strength following IMT were lower in participants who were older, when IMT was initiated >3 months following onset of COVID-19, and in participants with more severe dyspnoea at baseline; and *3)* for changes in perceived dyspnoea and health-related quality of life, there was large between-participant variability in both the IMT and control groups, but no evidence of heterogeneous IMT treatment effects.

This is the first investigation of heterogeneity in the *effectiveness* of an unsupervised, home-based exercise or physical activity intervention using appropriate statistical methods. Whilst several recent studies have been unable to detect heterogeneous treatment effects for body composition, cardiorespiratory fitness and blood pressure following *supervised* exercise training in adults (25–28), we found extremely strong evidence of individual responses for changes in inspiratory muscle strength following unsupervised IMT. This discrepancy is likely explained, at least in part, by the additional variability in intervention adherence and fidelity present in our study given its remote and unsupervised delivery method. Indeed, the improvements in inspiratory muscle strength were positively related to IMT characteristics, including number of training sessions, number of training breaths, the duration of training breaths, and total cumulative power over the intervention. Total cumulative power was the strongest predictor of changes in inspiratory muscle strength: for every 1 SD increase in total

cumulative power over the eight-week intervention, we observed a further improvement in MIP of 10.9 [95% CrI: 5.3-16.8] cm H_2O and a further improvement in SMIP of 63.7 [95% CrI: 32.2-95.3] PTUs. These data provide the clearest evidence of a dose-response relationship for improvements in inspiratory muscle strength following IMT. This finding can inform the delivery of IMT as a rehabilitative tool for post-acute COVID-19 syndrome, but it is likely that similar heterogeneity would also be observed with the delivery of home-based IMT in other chronic respiratory conditions where IMT has been shown to be beneficial for inspiratory muscle strength, such as chronic obstructive pulmonary disease (29), asthma (30) or cystic fibrosis (31). There are a wide range of individual, psychosocial, and disease-specific factors that influence adherence to home-based exercise (e.g., 32,33) and it will be important for future research to determine the potential barriers and facilitators that influence adherence to unsupervised home-based exercise in people with post-acute COVID-19 syndrome.

In comparison to previous studies of heterogeneity of exercise response, this study investigated a population living with a disease of highly diverse manifestation and aetiology (3,13). Our findings suggest this impacted the improvements in inspiratory muscle strength following IMT. Specifically, we found that more severe dyspnoea and initiating IMT >3 months following COVID-19 infection, were related to smaller improvements in inspiratory muscle strength. Such findings have implications for the timing of rehabilitation components, suggesting that IMT should be offered early in rehabilitation programmes to maximise its efficacy. Interestingly, whilst we observed a dose-response to IMT within the sample as a whole, there were no notable correlations between baseline dyspnoea (BDI score), time since COVID-19 infection, or age, and any IMT dose variable. This implies that the smaller improvements were due to differences in the physiological response to a given dose of IMT

in these subpopulations, rather than systematic differences in the quantity/quality of IMT exposure.

It is curious that we could detect evidence of meaningful heterogeneity of response for physiological outcomes (respiratory muscle strength) but not for subjective outcomes (perceived dyspnoea and health-related quality of life). It is, however, noteworthy that there was a high level of between-participant variability for these subjective outcomes in both the control and intervention group. This is perhaps unsurprising given the relapsing/remitting nature of post-acute COVID-19 syndrome symptomatology (3), together with evidence that subjective measures of dyspnoea can be unrelated to underlying disease severity and influenced by multiple other situational factors (e.g., emotional, behavioural, environmental; (34)). As such, the lack of observed heterogeneity in treatment response for these outcomes may be partly explained by the typical error of measurement generally being higher for the subjective, compared to the physiological, outcomes in our study. The typical error (20) expressed relative to the baseline standard deviation, was 0.45 for MIP, 0.35 for SMIP, and 0.54, 0.44, 0.76 and 0.62 for the KBILD breathlessness, psychological, chest, and total scores, respectively. Therefore, we cannot specifically rule out meaningful heterogenous treatment effects for these subjective outcomes, but high measurement error will inevitably mask any individual variability in the treatment group and make identification of potential moderator/mediator variables challenging. It is also important to note that there was a mean improvement in perceived dyspnoea (TDI score) with IMT compared to the control group (5). Thus, if prescribing IMT as a rehabilitative intervention, it would be prudent to aim to maximise improvements in clinically relevant physiological outcomes in the knowledge that some improvement in perceived dyspnoea will also likely be exhibited.

Practical Implications

MIP and SMIP as markers of respiratory muscle function are recognised as important clinical outcomes in people with pulmonary disease (14). IMT could be part of a therapeutic programme for people with pulmonary disease (29,30), including post-acute COVID-19 syndrome (5), and our findings demonstrate that prescription of unsupervised home-based IMT - the likely scenario for scalable real-world implementation - leads to heterogeneous responses for changes in respiratory muscle strength. A high proportion of people can be expected to see some change in respiratory muscle strength following IMT (~84% for MIP and ~95% for SMIP), but greater improvements are observed with a larger dose of IMT. Therefore, practitioners who are implementing IMT as a rehabilitation tool in people with post-acute COVID-19 syndrome should encourage patients to accumulate a larger dose of training to maximise improvements in inspiratory muscle strength. Our findings also provide the basis for future research to determine: 1) why older age, a longer time post-acute COVID-19 syndrome, and a greater severity of baseline dyspnoea, are associated with smaller improvements in inspiratory muscle strength following IMT; and 2) how IMT may be adapted to enhance the improvements in these subpopulations.

Limitations

Whilst there are numerous strengths of this study, certain limitations need to be acknowledged. Firstly, we applied conventional subgroup analysis to identify potential moderators of individual responses for respiratory muscle strength (7). Although this approach can identify theoretical conditions under which the intervention is most/least effective, there are limitations to its use to inform decision making at an individual level; individuals can belong to multiple different subgroups which may yield different inferences about the optimal treatment effect (7). There are also potential relationships between the mean and standard deviation of change scores (35), such that some of the apparent

heterogenous treatment effects in inspiratory muscle strength may reflect systematic changes in the intervention versus control group. Our population was also largely female and, although this is reflective of a higher female prevalence of post-acute COVID-19 syndrome (36), it was not possible to determine whether heterogeneity in response would be present in males, or whether biological sex is a potential moderator of the heterogeneity. It should also be noted that the questionnaires utilised in this study have not specifically been validated in people with post-acute COVID-19 syndrome. In addition, we took the decision to focus on dyspnoea and have not collected data on the range or severity of other symptoms that were experienced (3). Finally, as the data was collected entirely remotely and during periods of lockdown, there were limitations on the outcome measures able to be obtained. Whilst changes in MIP and SMIP are key markers of pulmonary function, it will be important to determine whether similar heterogeneity is present for other markers (e.g. diaphragm thickness, ventilatory reserve etc.).

Conclusions

We have previously reported that eight weeks of unsupervised home-based IMT resulted in *mean* improvements in perceived dyspnoea and inspiratory muscle strength in people with post-acute COVID-19 syndrome (5). The present findings provide additional novel insight by demonstrating that there is *individual variability* in the improvement in inspiratory muscle strength (but not perceived dyspnoea) following IMT in people recovering from COVID-19 (i.e., some people get more benefit, and some people get less benefit from the IMT intervention for inspiratory muscle strength). Consistent with standard exercise theory, larger improvements in clinically relevant markers of inspiratory muscle strength are strongly related to a greater cumulative dose of IMT over the intervention.

AUTHOR CONTRIBUTIONS

MAM and KAM conceived the idea for the primary RCT and were the grant holders and principal investigators. MAM, KAM, ZLS, GAD, KL, JD, RB, JH were involved in the design of the primary RCT. MM and JS collected the data for the primary RCT. RSM, MAM, KAM and PAS conceived the idea for this manuscript. PAS provided statistical expertise and performed the statistical analysis. RM wrote the initial draft of the manuscript. All authors were involved in drafting versions and critically revising for important intellectual content. All authors have read and approved the final version. MAM is the guarantor of the study.

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COMPETING INTERESTS

None to declare.

DATA AVAILABILITY STATEMENT

The deidentified data are available from the corresponding author upon reasonable request.

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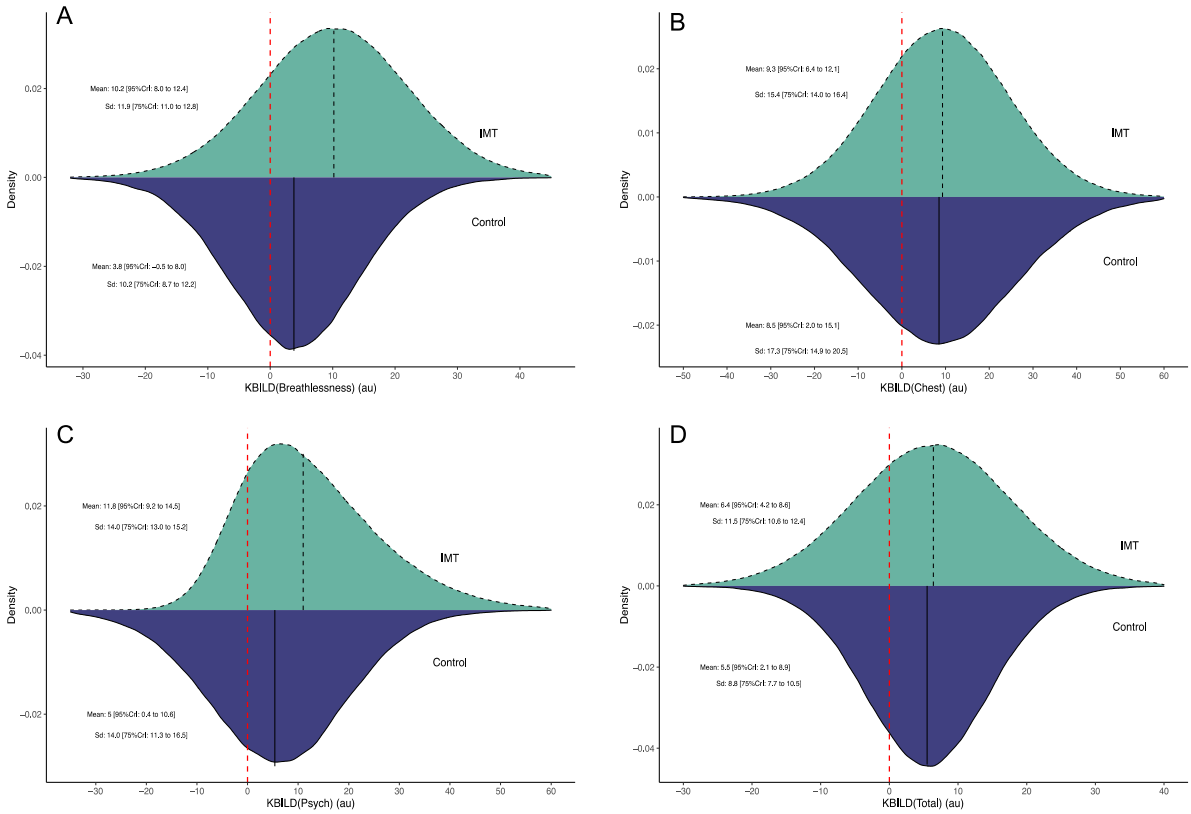

Figure 1: Distribution of change scores in KBILD Breathlessness (A), Chest (B), Psychological (C) and total (D) scores following IMT (green) and control (blue). Black vertical lines represent the estimated mean changes, and the dashed red line represents zero. KBILD: 15-item Kings Brief Interstitial Lung Disease; CrI: Credible interval.

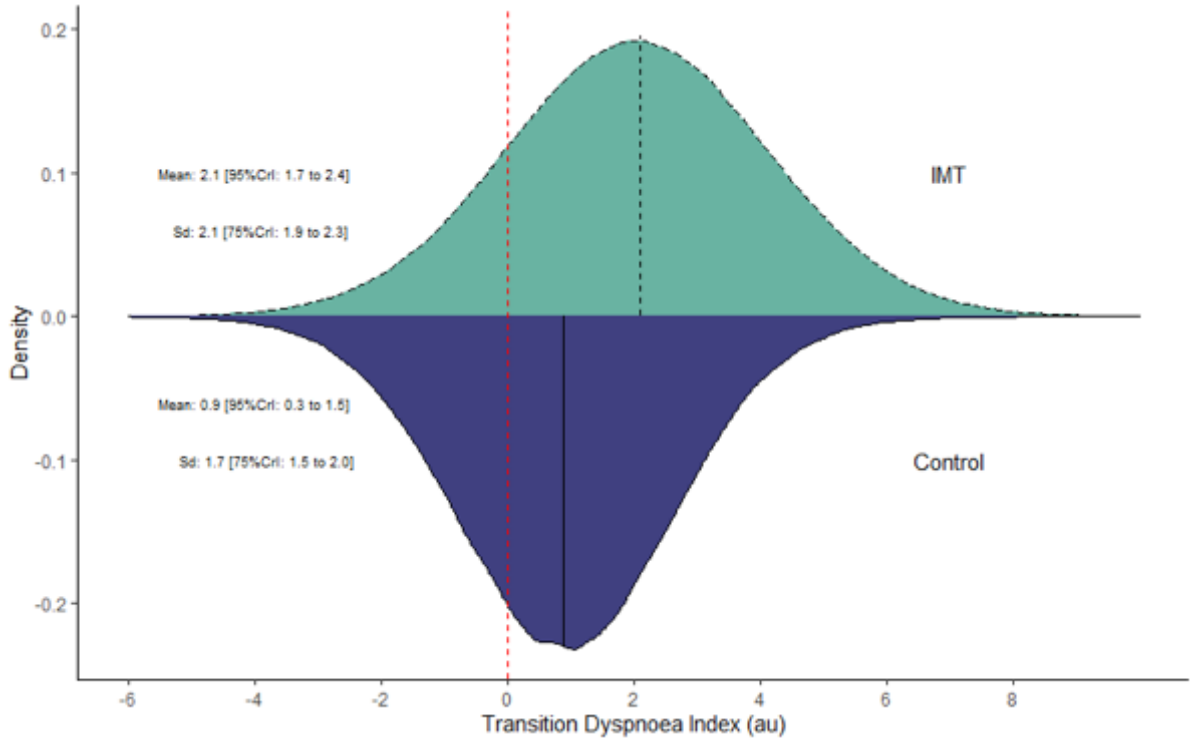

Figure 2: Distribution of Transition Dyspnoea Index scores following IMT (green) and control (blue). Black vertical lines represent the estimated mean changes, and the dashed red line represents zero. CrI: Credible interval.

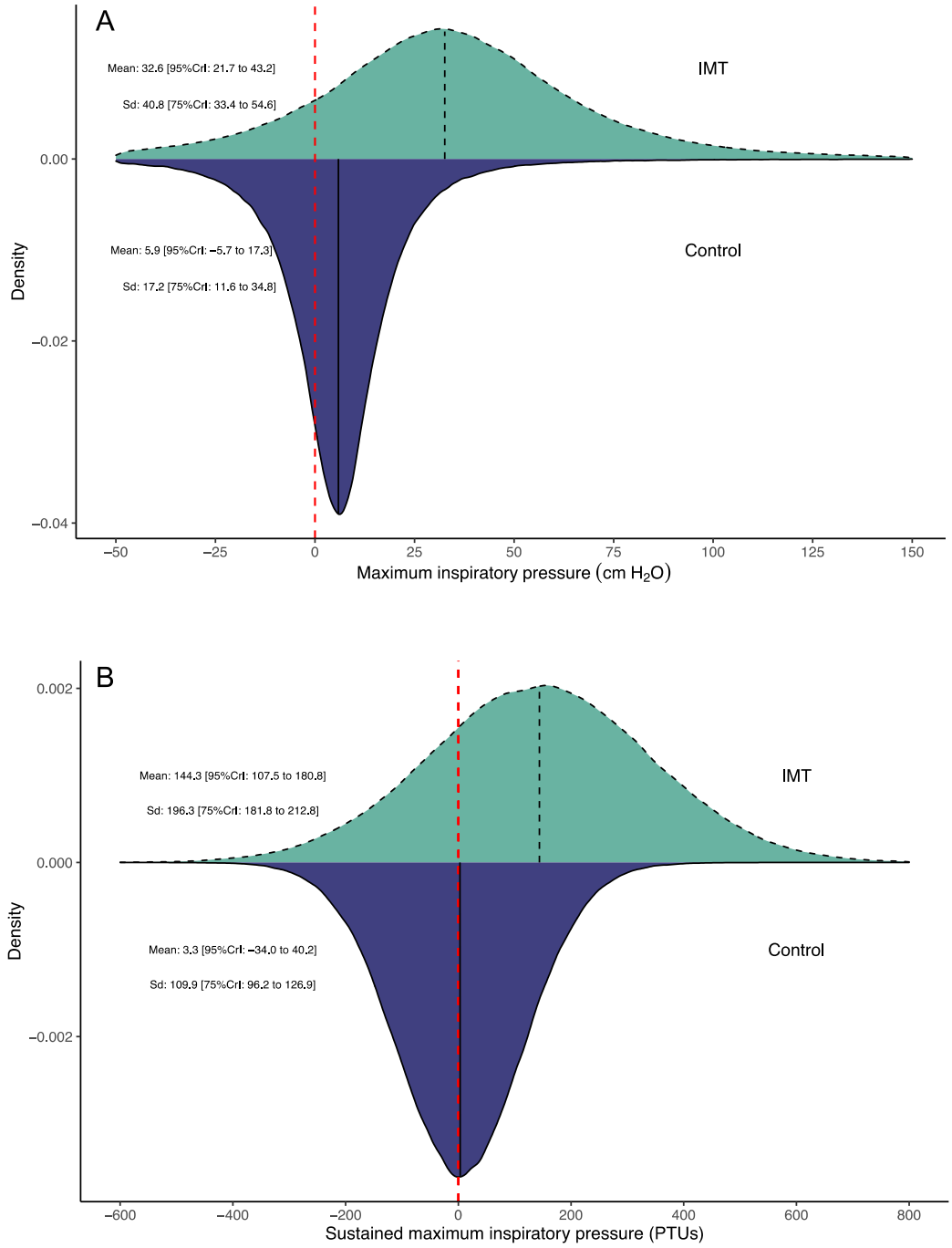

Figure 3: Distribution of change scores for maximal inspiratory pressure (A) and sustained maximal inspiratory pressure (B) following IMT (green) and control (blue). Black vertical lines represent the estimated mean changes, and the dashed red line represents zero. CrI: Credible interval.

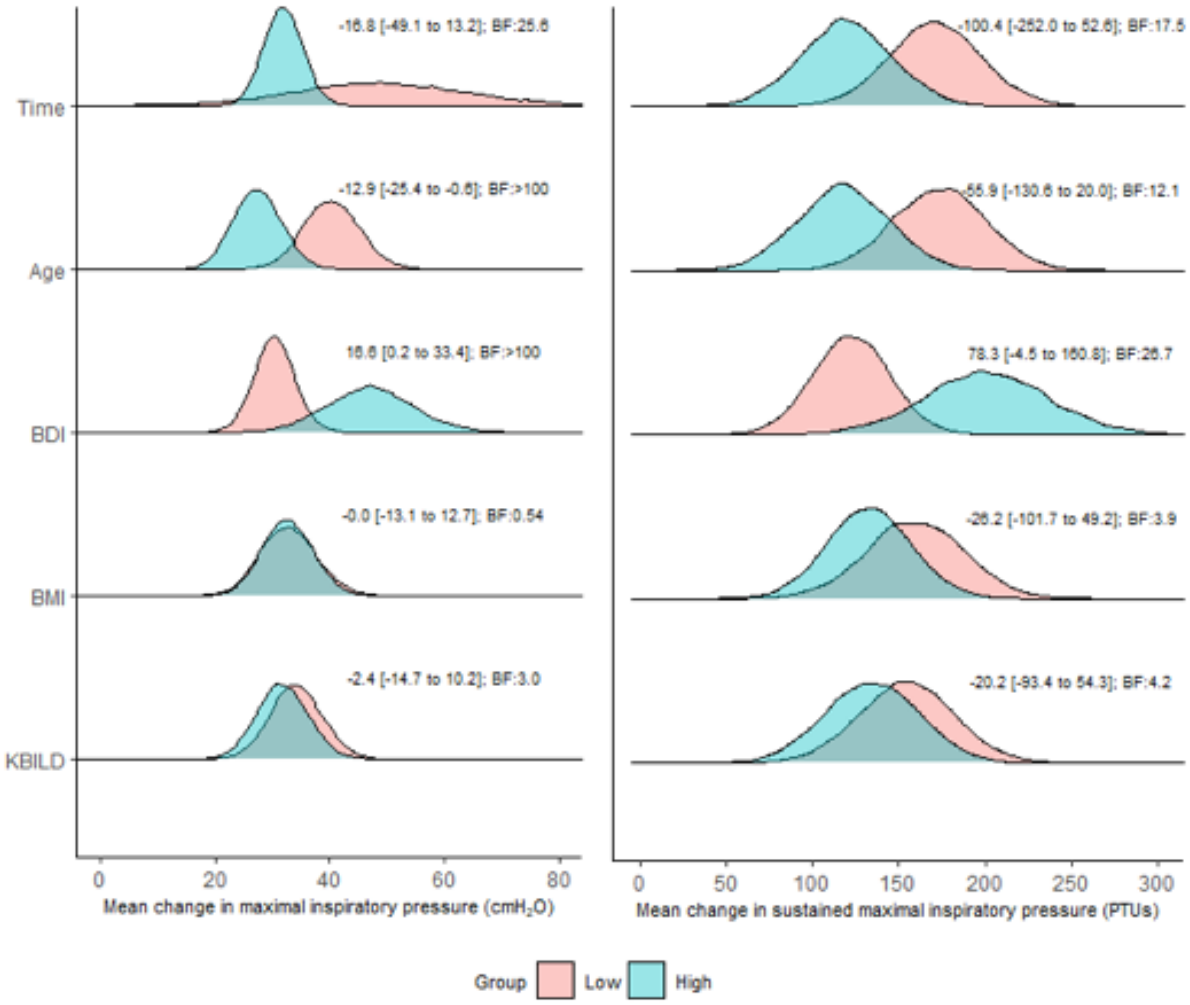

Figure 4: Density plots illustrating subgroup analyses of dichotomised participant characteristics exploring relative treatment effect modification for changes in maximal inspiratory pressure (left) and sustained maximal inspiratory pressure (right). Values and credible intervals provided estimate the difference in mean change following training between participants in the high relative to low group (positive values denote greater mean change in the high group). Time: time since COVID [low: ≤ 3months; high: >3 months]; Age [low:<50 years; high: ≥50 years]; BMI: Body Mass Index [low: <25 kg•m^{-2}; high: ≥25 kg•m^{-2}]; age [low:<50 years; high: ≥50 years] KBILD: 15-item Kings Brief Interstitial Lung Disease baseline total score [low: <53; high: ≥53]; BDI: Baseline Dyspnoea Index [low: ≤6 units; high: >6 units]); BF: Bayes factor.

Table 1 Participant characteristics

	IMT (*n*=111)	Control (*n*=36)
Males / Females	19 / 92	2 / 34
Age (y)	48 (11)	49 (12)
BMI ($kg•m^{-2}$)	27.8 (6.9)	27.5 (6.2)
Time since COVID-19 (months)	9.3 (3.6)	9.4 (3.2)
Baseline Dyspnoea Index	5.8 (2.5)	5.4 (2.9)

Data are shown as mean (SD) unless indicated otherwise.

Table 2: Variation in IMT Intervention Characteristics

Training Characteristic	Prescribed	Recorded		
		Median (IQR)	Min	Max
Total Sessions (*n*)	24	20 (6)	0	44
Frequency (mean sessions•week^{-1})	3	2.5 (0.750)	0	5.3
Total Breaths (*n*)	864	607 (357.6)	0	1565
Mean Breaths•Session^{-1} (*n*)	36	33.2 (8.35)	0	37.9
Mean Breath Duration (secs)	-	11.4 (4.6)	0	22.2
Cumulative Power (PTUs)	-	222,302 (187,338)	0	602,809
Cumulative Power: Baseline MIP	-	3,152 (2,867)	0	16,047
Cumulative Power: Baseline SMIP	-	525 (483)	0	2,245

SD: standard deviation; PTUs: pressure time units; MIP: maximal inspiratory pressure; SMIP: sustained maximal inspiratory pressure. IQR: Interquartile Range. Cumulative Power: Baseline MIP and Cumulative Power: Baseline SMIP were calculated by dividing Cumulative Power (PTUs) by baseline MIP and SMIP respectively.

Table 3: Assessment of heterogeneous treatment effects across dependent variables based on group change scores

Variable	Mean difference [95% CrI]	Standard deviation difference [75% CrI]	Bayes factor	Distribution	Proportion of response [95% CrI]
KBILD (Breathlessness) (au)	6.4 [-0.3 to 13.2]	1.7 [-1.3 to 4.3]	0.65	Normal distribution	NA
KBILD (Psychological) (au)	6.8 [-1.2 to 15.1]	-0.0 [-3.9 to 3.3]	0.41	Normal distribution	NA
KBILD (Chest) (au)	0.8 [-9.6 to 10.9]	-1.9 [-6.6 to 1.9]	0.54	Normal distribution	NA
KBILD (Total) (au)	0.9 [-4.9 to 6.6]	2.7 [0.2 to 4.9]	1.49	Normal distribution	NA
Transition Dyspnoea Index (au)	1.1 [0.2 to 2.1]	0.4 [-0.1 to 0.8]	0.94	Normal distribution	NA
Maximum inspiratory pressure (cm H_2O)	26.6 [10.5 to 42.7]	22.8 [4.7 to 37.7]	>100	T-distribution	0.84 [0.63 to 1.0]
Sustained maximum inspiratory pressure (PTUs)	141.2 [68.0 to 42.7]	86.8 [55.7 to 116.7]	>100	Normal distribution	0.95 [0.76 to 1.0]

Mean difference: Difference in the mean change score between IMT and control groups. Standard deviation difference: Difference in the standard deviation of change scores between IMT and control groups. Bayes factors: Values greater than 1 provide evidence for difference in the standard deviation of change scores between IMT and control groups. KBILD: 15-item King's Brief Interstitial Lung Disease. CrI: Credible interval. NA: Not applicable due to no clear evidence of heterogenous treatment effects.

Table 4: Assessment of relative treatment effect modification of training-related variables for changes in maximal and sustained maximal inspiratory pressure

Variable	Maximal inspiratory pressure (MIP)		Sustained maximal inspiratory pressure (SMIP)	
	β Change Score [95%CrI:]	Bayes Factor	β Change Score [95%CrI:]	Bayes Factor
Number of sessions (*n*)	2.7 [-3.0 to 8.7]	6.5	5.6 [-28.8 to 39.0]	5.9
Total breaths (*n*)	5.3 [-0.4 to 11.3]	37.8	15.7 [-17.1 to 50.1]	43.2
Mean breaths per session (*n*)	8.3 [2.5 to 14.0]	>100	26.1 [-7.9 to 59.4]	96.9
Breath duration (s)	4.8 [-1.7 to 11.1]	25.4	25.8 [-7.4 to 60.1]	85.1
Cumulative Power (PTUs)	10.9 [5.3 to 16.8]	>100	63.7 [32.2 to 95.3]	>100
Cumulative Power: Baseline MIP	14.3 [7.9 to 21.0]	>100	57.9 [25.0 to 90.6]	>100
Cumulative Power: Baseline SMIP	9.8 [4.4 to 15.5]	>100	90.2 [61.4 to 120.0]	>100

Training variables were standardised such that β represents the expected increase/decrease in the dependent variable change scores for a standard deviation increase in the training variable. CrI: Credible interval; PTUs: pressure time units. Cumulative Power: Baseline MIP and Cumulative Power: Baseline SMIP were calculated by dividing Cumulative Power (PTUs) by baseline MIP and SMIP respectively.