

Cognitive and behavioral processes predict anxiety and depression in patients with pulmonary hypertension

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Abstract

Emotional and psychological difficulties cannot fully be explained by disease-related factors in people with pulmonary hypertension (PH). This study examined the relationship between anxiety, depression, demographic, objective and subjective PH factors, and self-reported cognitive and behavioral processes, which have been associated with mood in clinical and nonclinical samples. This is a secondary analysis of baseline data from 77 adults with PH who took part in a randomized controlled trial of a self-help intervention targeting anxiety in PH. Participants completed self-report measures including: demographic (age, gender, ethnicity, education, employment) and clinical questionnaire (PH diagnosis, functional class, years since diagnosis), depression (PHQ-9), anxiety (GAD-7), health-related quality of life (emPHAsis-10), dyspnea (D12), and cognitive and behavioral processes (CBP-Q) scale. Data were analyzed using correlational and regression analyses. Overall, 70% and 63% of participants scored above the clinical cut off for anxiety and depression, respectively. Demographics were not associated with anxiety or depression. PH-related factors were correlated with depression but not anxiety. A multiple regression analysis suggested dyspnea and cognitive processes significantly predicted anxiety whereas behavioral processes were not a unique predictor. In contrast, dyspnea and behavioral processes predicted depression whereas cognitive processes did not. While a body of evidence exists demonstrating people with PH are more likely to experience anxiety and depression, less is known about factors that cause and maintain these disorders. Findings highlight the significance of subjective factors that could be a target for screening and psychological treatments for emotional difficulties, such as cognitive behavioral therapy.

KEYWORDS

cognitive behavioral therapy, mood, psychological therapy, pulmonary arterial hypertension, treatment

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INTRODUCTION

Pulmonary hypertension (PH) is a heterogeneous group of serious conditions associated with elevated pulmonary artery pressure. Five groups of the condition are recognized: pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to lung disease, PH due to blood clots in the lung otherwise known as chronic thromboembolic (CTEPH), and PH due to unclear or multifactorial mechanisms.¹ Symptoms of PH can vary with common self-reported difficulties including shortness of breath, fatigue, chest pain, palpitations, syncope or near-syncope, and edema.² Despite advancements in treatments,³ most forms of the disease are experienced as progressive, life shortening and debilitating.^{4,5}

There is growing evidence demonstrating this patient group are more likely to report lower health-related quality of life (HRQoL),⁶ emotional difficulties⁷ and psychological comorbidities,^{8,9} including anxiety and panic disorders, and depression.^{10,11} More specifically, a recent systematic review by Mai et al., examining the prevalence, risk factors and treatment effectiveness for anxiety and depression in PH involving over 2100 patients from around the world reported that rates are alarmingly high. The pooled prevalence of depression was 28% (95% confidence interval [CI]: 20.5–36.8) and anxiety was even higher at 37.1% (95% CI: 28.7–46.4).¹² The picture is more concerning with evidence suggesting only the minority of patients with anxiety and/or depression and PH receive support.^{13–15} Anxiety and depression are typically highly comorbid in PH and both conditions have been shown to have a significant impact on HRQoL.¹⁶

Identifying risk factors for anxiety and depression is an important agenda as it will help to identify those who may experience (or are currently suffering from) mood disorders, inform our understanding of how people with PH develop anxiety and depression, and highlight targets for intervention.¹⁷ Most of the research in this area has focused on disease-related and objective factors, such as pulmonary vascular resistance; PH diagnosis; World Health Organisation functional classification system, which ranges from I to IV; or demographics including age, marital status and financial circumstance.^{4,12} Of the factors commonly investigated, few have been found to be a significant predictor, with Mai et al. examining 20 possible factors identifying only two significant predictors of depression (PAH—congenital heart disease and CTEPH) and three for anxiety (PAH—congenital heart disease, pulmonary vascular resistance, and cardiac index).¹² It is therefore unsurprising that authors have suggested disease severity alone is insufficient to fully explain psychological difficulties such as mood disorders in people with PH.⁴ In contrast, there is a lack of evidence concerning subjective risk factors, such as

measures of psychological functioning or distress. In other long-term conditions, self-reported measures have been found to be significant predictors of anxiety and depression^{18,19}—and in fact, in some disorders, self-report measures of functioning can account for a greater variance than disease-related factors.²⁰

The aim of this study was to examine the relationship between anxiety, depression, and self-reported psychological processes using the Cognitive Behavioral Processes Questionnaire (CBP-Q)²¹ in individuals with PH. The CBP-Q was initially developed to investigate attention, memory/imagery, thinking, reasoning and behaviors such as avoidance, inactivity or substance use that are believed to maintain distress in those with psychological disorders. Indeed, the CBP-Q has since been found to be associated with anxiety and depression in clinical and nonclinical samples. Another reason why this measure was utilized was because it was designed with the intention of being used alongside Cognitive Behavioral Therapy (CBT). Measures investigating proposed mechanisms of change associated with psychological therapy can help to highlight which skills clients need to develop or focus on, and understand why some individuals improve with treatment (and some do not).²² CBT is a form of psychological therapy that aims to help people change the way they think and how they act. CBT is one of the most researched forms of psychological therapy and recommended by clinical guidelines for treating most mental health difficulties, including anxiety and depression^{23,24}—however there is a paucity of research investigating CBT in people with PH.^{10,11,25}

We hypothesized that anxiety and depression would be significantly correlated with self-reported measures of distress and psychological processes, namely dyspnea and cognitive and behavioral processes. Given the mixed evidence examining the link between demographics and PH-factors and anxiety and depression in this clinical group, we did not make any specific predictions regarding these factors. Second, we expected cognitive and behavioral processes to be a unique predictor of anxiety and depression after controlling for PH specific measures (i.e., self-report breathing difficulties). This is consistent with research suggesting disease-related factors do not fully explain anxiety and depression in people with PH.

METHODS

Participants

Participants were initially recruited for a randomized controlled trial investigating a self-help intervention targeting anxiety in adults (18 years) living with PH.²⁵

The intervention was based on CBT, consisting of four booklets that participants were asked to complete weekly. Participants were either randomized to the intervention ($n = 37$) or a wait-list control condition ($n = 40$). Data presented in the current study have been extracted from participants' baseline (preintervention) data.

Participants must have been aged 18 years or older, have a diagnosis of PH (all forms were accepted), be able to complete questionnaires in English without help and self-report having difficulty with anxiety. Individuals could not be experiencing thoughts of self-harm or suicide. Participants provided written consent for their data to be used for the purpose of additional research. Initial ethical consent was obtained from the University of Sheffield (034442).

Recruitment

Participants were recruited via PHA around the world, including PHA UK. Participants responded to an advert from PHA. Participants were first asked to read a participant information sheet before being asked to complete a consent form and series of questionnaires (see below).

Measures

Self-reported demographic (age, gender, ethnicity, years of education, type of employment) and clinical information relating to PH (years since diagnosis of PH, PH diagnosis and functional class). Individuals were not asked to self-diagnose their condition, but report whether they were aware of their type of PH and functional class. Participants were given the option of selecting "not sure" if they did not know.

Anxiety was measured using the Generalized Anxiety Disorder-7 (GAD-7) questionnaire.²⁶ Participants were asked to report how often over the last 2 weeks had they been bothered by seven anxiety-related difficulties using a four-item Likert scale. Scores range from 0 to 21. The clinical cut-off score is ≥ 8 . Cronbach's α was 0.91.

Depression was measured using the Patient Health Questionnaire-9 (PHQ-9).²⁷ Respondents were asked to rate on a four-item Likert scale how often over the last 2 weeks had they been bothered by nine depression-related difficulties. Scores range from 0 to 29, with ≥ 10 representing the clinical cut-off. Cronbach's α was 0.84. The GAD-7 and PHQ-9 are the some of the most commonly used measures of anxiety and depression in people with PH.¹²

HRQoL was examined using the emPHAsis-10 which is a condition specific measure.²⁸ Scores range from 0 to 50, with a higher score indicative of lower HRQoL. Participants were asked to rate on a six-item Likert scale, how much they had recently experienced 10 PH-related challenges. Cronbach's α was 0.89.

Self-reported difficulties with breathing were explored using the Dyspnea 12 (D12).²⁹ Total scores range from 0 to 36, with a higher score indicating greater difficulty. Participants were asked to rate 12 questions in relation to their breathlessness "these days," on a four-item Likert scale. Cronbach's α was 0.95.

The CBP-Q asks participants to rate 15 items using a nine-item Likert scale, the responses of which differ depending on the question asked. Higher scores are associated with more unhelpful cognitive and behavioral responses, which have been found to positively relate to anxiety and depression symptomatology. Scores for cognitive processes (eight items) range from 0 to 64, and behavioral processes (seven items) 0–56.²¹ Cronbach's α for the cognitive items was 0.81 and behavioral 0.69.

Data analysis

Descriptive statistics were used to describe the sample. Preliminary correlational analyses were first performed using Pearson's correlation to examine the relationship between anxiety and depression and demographic (age, gender, ethnicity, years of education, type of employment), PH specific measures (years since diagnosis, PH diagnosis, functional class, self-reported dyspnea and HRQoL) and finally, psychological factors (cognitive and behavioral processes). Next, hierarchical multiple regression analyses were conducted with anxiety and depression as outcome variables, and with predictor variables entered in the order of demographic, PH objective measures, PH subjective measures and finally, self-reported psychological measures (cognitive and behavioral processes). This order was chosen for two reasons: (i) to assess the contribution of subjective measures after disease-related factors had been controlled for, and (ii) because less is known about the contribution of self-reported measures on anxiety and depression in this population. HRQoL was not included as it was viewed as an indicator of general functioning rather than a unique predictor or symptom. Factors that were not significantly associated with anxiety or depression were not included in the regression analyses. An α value of 0.05 was used for all statistical analysis. Data was analyzed using SPSS 26.

TABLE 1 Information on participant's demographic, PH specific factors and results of self-reported clinical measures ($n = 77$)

	Mean (SD)	N (%)
<i>Demographics</i>		
Age	47.82 yrs (13.46)	
Gender		
Female		72 (93.5)
Male		4 (5.2)
Other		1 (1.3)
Ethnicity		
White		45 (58.4)
Asian		9 (11.7)
Hispanic		1 (1.3)
Black		1 (1.3)
Latina		2 (2.6)
Not reported or not clear		19 (24.7)
Education	15.42 yrs (4.22)	
Employment		
Employed		27 (35.1)
Not employed		22 (28.6)
Retired		18 (23.4)
Student		3 (3.9)
Other		7 (9.1)
<i>PH specific factors</i>		
Duration of PH	8.63 yrs (8.82)	
Functional class		
I		8 (10.4)
II		17 (22.1)
III		27 (35)
IV		2 (2.6)
Not sure		23 (29.9)
PH diagnosis		
Idiopathic PAH		35 (45.5)
Chronic thromboembolic PH		14 (18.2)
Connective tissue disease		6 (7.8)
Congenital heart disease related PAH		4 (5.2)
Familial PH		1 (1.3)
Other		9 (11.6)
Not sure		8 (10.4)

TABLE 1 (Continued)

	Mean (SD)	N (%)
<i>Self-report clinical measures</i>		
Dyspnea	15.51 (9.43)	
HRQoL	39.94 (11.02)	
Anxiety	11.12 (5.48)	
Above clinical cut off 8		70.1%
Depression	12.55 (5.56)	
Above clinical cut off 10		63.6%
<i>Psychological factors</i>		
Cognitive factors	38.91 (10.02)	
Behavioral factors	30.16 (8.37)	

Abbreviations: PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; Yrs, years.

RESULTS

Participants

Overall, data from 77 participants were analyzed with different forms of PH and functional classes (Table 1). The majority were female and self-reported as white. Participants had been diagnosed with PH for 8.6 years on average, although a large variance was observed. Overall, 57% of participants self-reported having either type II or III functional class symptoms with the majority being diagnosed with idiopathic PH or CTEPH. Over 70% scored above the clinical cut off for anxiety and 63% for depression.

A summary of correlational analyses is shown in Table 2. Results indicate that none of the demographic measures investigated were significantly associated with anxiety or depression scores. Functional class and type of PH were significantly associated with depression ($p < 0.05$) and HRQoL, whereas no PH specific factors were associated with anxiety. Self-reported measure of dyspnea was significantly positively correlated with anxiety and depression. There was also a significant relationship between cognitive and behavioral processes and anxiety and depression, with more helpful behaviors and cognitions associated with fewer difficulties. Interestingly, dyspnea was not correlated with cognitive or behavioral factors. As expected, anxiety, depression and HRQoL were significantly correlated, as were dyspnea and HRQoL.

A hierarchical multiple regression with anxiety as the outcome variable revealed dyspnea explained 12% of the

TABLE 2 Correlation between anxiety (GAD-7) and depression (PHQ-9) and demographic, PH specific factors and psychological self-reported measures

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Anxiety	1													
2. Depression	0.65***	1												
3. Age	−0.2	0.16	1											
4. Gender	0.1	0.01	0.27*	1										
5. Ethnicity	0.06	0.18	−0.3*	−0.12	1									
6. Education	−0.07	−0.13	0.03	−0.07	0.05	1								
7. Employment	−0.11	0.03	0.24*	0.17	−0.2	−0.04	1							
8. Duration of PH	0.06	0.13	−0.07	0.05	0.11	0.12	0.28*	1						
9. Functional class	0.18	0.31*	0.2	0.14	−0.06	0.07	0.17	0	1					
10. PH diagnosis	0.17	0.29*	−0.09	−0.17	0.19	0.07	−0.14	0.19	0.23	1				
11. Dyspnea	0.37**	0.59***	0.26*	0	0.01	−0.09	0.11	−0.04	0.41**	0.14	1			
12. HRQoL	0.4***	0.71***	0.21	−0.07	0.06	−0.1	−0.15	0	0.52***	0.27*	0.73***	1		
13. Cognitive factors	0.5***	0.47***	−0.1	−0.11	0.15	0.06	−0.17	−0.11	0.08	0.22	0.15	0.2	1	
14. Behavioral factors	0.47***	0.48***	−0.16	−0.11	0.23	−0.03	−0.15	−0.06	0.17	0.18	0.2	0.3*	0.66***	1

Abbreviations: HRQoL, health-related quality of life; PH, pulmonary hypertension.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

variance with cognitive and behavioral factors explaining a further 22.8%. The final model accounted for 35% of the variance, of which dyspnea and cognitive processes were significant predictors—behavioral factors did not reach significance ($p = 0.11$).

In the model with depression as the outcome variable, PH diagnosis and functional class were significant predictors, accounting for 21% of the variance. Dyspnea added further 21%, with PH diagnosis and dyspnea remaining significant. In the final model, all factors accounted for 57% of the variance; however, only dyspnea and behavioral factors remained significant (Table 3).

DISCUSSION

While there is growing evidence to suggest adults with PH are at a higher risk of experiencing anxiety and depression,¹² very little is known about the potential causes and factors that may make people with PH more vulnerable to developing mood and anxiety disorders— notwithstanding what has been gleaned from qualitative findings.¹⁷ Most investigations in this area have focused on objective factors,¹² whereas in other medical conditions, self-reported measures have been extensively researched as possible predictors of mood difficulties.

Our hypotheses have been confirmed, with the findings suggesting that in adults with all forms of PH,

self-reported measures of breathing difficulties and cognitive and behavioral processes were correlated with anxiety and depression. Furthermore, after controlling for disease-specific difficulties (breathing difficulties, functional class and diagnosis), cognitive and behavioral measures explained a significant proportion of the variation of anxiety and depression. Results support the small number of studies demonstrating the use of psychological interventions targeting the sequelae of PH.^{25,30-32}

None of the demographic factors investigated were significantly related to anxiety and depression, which is in line with the systematic review of risk factors conducted by Mai et al.¹² Results are further consistent as, similar to Mai et al., we found type of PH was associated with depression. In contrast, Mai et al. found a relationship between a form of PAH and anxiety—the fact that we did not find an association may be explained by the modest number of participants with different types of PH which form the current sample. Another inconsistent finding was that we reported an association between functional class and depression whereas the review did not. That said, functional classes were grouped into I–II and III–IV in the review, which may have reduced sensitivity of the analysis.

It is important to note that the number of participants scoring above the clinical cut off for anxiety (70.1%) and depression (63.6%) exceeded the pooled prevalence

TABLE 3 Results of the hierarchical multiple regression analyses examining significant correlates of anxiety measured by the GAD-7 ($n = 75$) and depression measured using the PHQ-9 ($n = 49$) (listwise analysis)

	<i>B</i>	β	ΔR^2
<i>Anxiety</i>			
1			0.12**
Dyspnea	0.2	0.34**	
2			0.35***
Dyspnea	0.15	0.25*	
Cognitive processes	0.17	0.32*	
Behavioral process	0.24	0.21	
<i>Depression</i>			
1			0.21**
PH diagnosis	0.9	0.29*	
Functional class	2.2	0.3*	
2			0.42***
PH diagnosis	0.78	0.26*	
Functional class	0.15	0.02	
Dyspnea	0.32	0.54***	
3			0.57**
PH diagnosis	0.63	0.21	
Functional class	0.26	0.04	
Dyspnea	0.25	0.43**	
Cognitive processes	0.04	0.08	
Behavioral processes	0.21	0.34*	

Abbreviations: β , standardized beta; *B*, unstandardized beta; PH, pulmonary hypertension; ΔR^2 , increase in the model R^2 because of additional predictors.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

reported by Mai et al.¹² This finding is more than likely a reflection of our sample, who were initially recruited for an intervention designed for people self-reporting difficulties with anxiety.²⁵ Given the strong association between anxiety and depression observed in this sample and elsewhere,¹³ it also makes sense that rates of depression were high. Moreover, scoring above the clinical cut off on the screening measures is not a diagnosis but rather suggests people may benefit from consulting with a medical professional. Nevertheless, results suggest that routine screening for mood disorders in this population is indicated, assessing both anxiety and depression.

It was interesting to find that self-reported dyspnea predicted anxiety and depression but was not correlated with cognitive and behavioral processes—and remained

a significant predictor once these factors were added into the regression model. We are only aware of our study investigating a self-help intervention based on CBT for anxiety in people with PH, which examined the effectiveness of psychological therapy in this population measuring self-reported breathing difficulties as an outcome (D12), in which we found no change in dyspnea scores ($p = 0.01$).²⁵ In other conditions associated with breathing difficulties such as chronic obstructive pulmonary disease, a review including two studies on CBT had a small effect on improving dyspnea intensity (effect size 0.08–0.25) and moderate effect on dyspnea mastery (0.26–0.65); however, these treatments had a specific focus on the link between breathing difficulties and mood.³³ This suggests interventions for anxiety and depression should be delivered alongside treatments focusing on PH driven symptoms such as breathing difficulties and vice versa, recognizing people with dyspnea are likely to also report difficulties with mood.

Depression was related to more PH specific factors including breathing difficulties, functional class and type of PH and HRQoL specific to PH, compared to anxiety. Combined with the finding that behavioral processes were a significant predictor of depression (but not anxiety), whereas cognitive factors predicted anxiety (but not depression), it may be that low mood in people with PH is more linked with the limiting impact of the condition in terms of reduced physical health and fatigue, loss, isolation, and restricted daily activity.¹⁷ This is consistent with a study involving 64 patients with PH from Spain. Using a logistic regression analysis, PH symptoms significantly predicted clinically significant symptoms of depression (but not anxiety), whereas optimism, which examine people's beliefs about the future, predicted anxiety but not depression.⁴ Research has also shown that in people with PH, depressive symptoms are associated with higher levels of brain natriuretic peptide (a biomarker of heart failure and therefore a possibly indicator of physical ability),³⁴ as well as number of steps measured using an accelerometer—whereas anxiety was not.³⁵

Taken together, this hints at the possibility of different therapeutic targets focusing on behavioral factors for depression and cognitions for anxiety in this population. Indeed, research has shown behavioral activation (BA) for depression is just as effective as CBT. BA is an active ingredient of CBT; however, it is less intensive and can be easier to administer, as it can be cheaper and does not need to be delivered by specialized professionals.³⁶ People with depression typically become inactive, which reduces the opportunity for engaging in helpful experiences and activities that are rewarding, thus lowering the likelihood of feeling positive emotions

and a sense of mastery. BA looks to break this vicious cycle through increasing levels of activity. PH-related difficulties, such as pain, fatigue and breathlessness associated with physical activity may be the very reason for a reduction in activity in the first place.³⁷ This would help to explain the link between PH specific measures and depression. Strategies focusing on education, improving motivation,³⁸ pacing to help break activities up, build stamina and promote a balance between rest and activity—as a standalone or supplementary intervention—could be helpful.³⁹

In contrast, interventions aimed at the cognitive difficulties associated with PH, including rumination, thinking biases and worry, could be a focus when targeting anxiety. Indeed, unlike depression which may be more related to the severity of PH, the link between anxiety and PH may be better explained by factors influencing cognitions, such as coping skills to manage internal and external stressors and support from others.¹⁶ Future research is needed to examine moderating and mediating variables of the relationship between the condition and its impact, which could help highlight the role and support the use of different interventions.

It is a limitation that the current study was cross-sectional in design and therefore causation cannot be inferred. However, the current results should be viewed in the context of the findings from our randomized controlled trial, which generated evidence to suggest changes in cognitive and behavioral processes (as measured by the CBP-Q) mediated a treatment related reduction in anxiety and depression.²⁵ Combined, the findings from our two studies show that cognitive and behavioral processes are a predictor of anxiety and depression and therefore should be considered when healthcare professionals are screening patients with PH for emotional difficulties, as well as a target for treatment. That being said, it should be recognized that the CPB-Q only measures factors associated with CBT treatments for anxiety and depression. It does not account for some of the other difficulties that CBT has been shown effective for, such as pain and fatigue, which are also common in PH. What is more, we were unable to investigate the impact of other PH-related difficulties that could have an impact on anxiety and depression such as medical treatments and their side-effects, and type of PH. This will need further investigation; for example, a similar study focused specifically on individuals with PAH may be of benefit and add further insight given there are a range of therapies available with varying complexity for this clinical group, which might impact on cognitive and behavioral processes. Future research utilizing a longitudinal design is also required to examine predictors for the development of anxiety and depression

in this clinical group. While the sample size is similar to other studies in this area, it is modest. Nevertheless, it is a strength that the sample is heterogeneous and characteristic of people in the community with PH who are experiencing and have sought help for difficulties with mood. Finally, as we recruited people from the community, we were unable to confirm their diagnosis of PH, instead relying on participants confirming that they had been given a diagnosis of PH. However, we believe it is unlikely that any participants did not have PH, given that we recruited people who were using a service specific for PH, PHA UK. Similarly, we asked participants to disclose their type of PH and functional class also providing the option of “not sure” to avoid the risk of self-diagnosing. To help reduce the risk of reporting errors, we could have recruited people from medical settings where we would have had access to medical records including their medication regimens or PH registers—which may have allowed us to also examine the impact of treatment on depression and anxiety. While it may be helpful to undertake additional research to confirm the current findings in a sample recruited via such methods, it is a strength of this study that participants were recruited from the community. Indeed, the fact we did not use any PH-related factors or severity of anxiety as an exclusion may mean that we can more easily generalize the findings to this clinical population as opposed to a sub-group who were seeking healthcare for PH—however this would need to be verified in further studies.

In conclusion, subjective measures of functioning and psychological processes can help us to better understand anxiety and depression in people with PH and have implications for practice and service provision. Anxiety and depression were not related to any demographic factors, suggesting these difficulties can impact all individuals with PH. Future research is required to develop methods to screen and treat psychological difficulties that are highly prevalent in this clinical group. Our findings contribute to the small but growing evidence demonstrating the importance of psychological interventions, in particular CBT, recognizing the need to tailor treatments taking into considering the nature of emotional difficulties and how they interact with PH.

AUTHOR CONTRIBUTIONS

Gregg H. Rawlings developed the concept of the study and was involved in data collection, analysis and write up. He approved the final manuscript for submission. Andrew R. Thompson was involved in the initial randomized control trial supporting its conception and data analysis. He also provided comments on earlier manuscripts of the current paper and approved the final

version for submission. Iain Armstrong was involved in the initial randomized control trial supporting its conception and data analysis. He also provided comments on earlier manuscripts of the current paper and approved the final version for submission. Barbora Novakova was involved in the current data analysis and write up. She approved the final version for submission. Nigel Beail was involved in the initial randomized control trial supporting its conception and data analysis. He also provided comments on earlier manuscripts of the current paper and approved the final version for submission.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available upon reasonable request.

ETHICS STATEMENT

Initial ethical consent was obtained from the University of Sheffield (034442).

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