Understanding the effectiveness of different exercise training programme designs on VO_{2peak} in COPD: a component network meta-analysis

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ABSTRACT

Pulmonary rehabilitation programmes including aerobic training improve cardiorespiratory fitness in patients with COPD, but the optimal programme design is unclear. We used random effects additive component network meta-analysis to investigate the relative effectiveness of different programme components on fitness measured by VO_{2peak} in COPD. The included 59 studies involving 2191 participants demonstrated that VO_{2peak} increased after aerobic training of at least moderate intensity with the greatest improvement seen following high intensity training. Lower limb aerobic training (SMD 0.56 95% CI 0.32;0.81, intervention arms=86) and the addition of non-invasive ventilation (SMD 0.55 95% CI 0.04;1.06, intervention arms=4) appeared to offer additional benefit but there was limited evidence for effectiveness of other exercise and non-exercise components.

Pulmonary rehabilitation (PR) is an accepted treatment for COPD demonstrating improvements in peak oxygen uptake (VO_{2peak}), the gold standard measure of cardiorespiratory fitness.[1] However, PR is a complex intervention with significant variation in design and delivery across settings and the optimal programme design remains uncertain.[2] Furthermore, there is substantial heterogeneity in response to PR in both clinical trials[3] and real world clinical practice[4] which is only partially explained by differences in disease severity.[1] It is possible that some of the heterogeneity in response could be explained by variation in PR design.

Previous pairwise meta-analyses have examined individual elements of PR in isolation including the volume and modality of training as well as the addition of non-exercise components.[5–7] While this approach may give useful information, a pairwise meta-analysis can only include homogeneous trials in which a single component of PR programme design varies between treatment arms, and therefore ignores the wider complexity of PR. Component network meta-analysis (CNMA) is a novel statistical technique which allows inclusion of differing intervention designs in a single analysis to increase the power to detect differences in the effectiveness of individual components.[8] CNMA assumes the effects of individual components within complex interventions are additive and therefore allows estimation of the individual effect of each component in isolation.

Our previous systematic review demonstrated a moderate improvement in VO_{2peak} for people with COPD following a programme that included aerobic exercise training.[1] We performed a secondary analysis on this data using CNMA to investigate the effect of specific exercise and non-exercise components on improvements in VO_{2peak}.

METHODS

This is an extended analysis of data from a previous systematic review, full methods of which are detailed elsewhere[1] including prospective registration on PROSPERO (CRD42018099300). A comprehensive database search was performed based on 'COPD', 'exercise training' and 'VO_{2peak}' from inception to April 2018. The eligibility criteria for inclusion were a diagnosis of COPD in≥90% of the population, an intervention group performing directly supervised lower limb aerobic training, at a minimum frequency of once a week for at least 3 weeks and a direct measure of VO_{2peak} using any exercise modality. The current analysis was limited to both controlled trials comparing an intervention incorporating supervised lower limb aerobic training with no training, and controlled trials comparing different interventions for which supervised lower limb aerobic training was a component.

A frequentist random effects additive CNMA was performed using the netmeta package in R (version 4.1.1). We created two models: Model 1, a model with traditional lower limb aerobic training modalities combined in a single component to investigate the effects of non-aerobic exercise components and Model 2, a split model comparing different lower limb aerobic training components.

We performed multiple sensitivity analyses by excluding studies at high risk of bias and studies of low quality, and with imputation of data using a conservative estimate of correlation coefficient (0.5). To examine inconsistency, unconnected studies were excluded to create connected networks and results from net heat plots[9] and node splitting were assessed.

RESULTS

Fifty-nine studies involving 2191 participants were included (eTable 1). These included 15 trials of aerobic training vs "usual care" or structured education in isolation, 37 controlled trials in which both arms performed aerobic training in different forms or with different "add-ons", and seven 3-arm

Figure 1 Network graph showing comparisons made in studies included in the component network metaanalysis for type of aerobic training (model 2). The size of each node is proportional to the number of studies including that intervention and the thickness of the lines is proportional to the number of times each comparison was made. : interval training, : continuous training, : cycling, : walking, High: high intensity, Mod: Moderate intensity, UC: Usual care.

studies with three interventions or two interventions vs "usual care". Of these, 50 studies were included in Model 1 (eFigure 1) and 30 studies were included in Model 2 (figure 1).

Lower limb aerobic training, non-invasive ventilation (NIV) during exercise and administration of ghrelin alongside exercise training resulted in significant improvements in VO_{2peak} (figure 2). No other components provided additional benefit when performed alongside lower limb aerobic training. Both moderate to high intensity continuous cycling and walking training modalities, and high intensity interval cycling and walking resulted in improvements in VO_{2peak} (all $p<0.05$, figure 3). Addition of stair climbing (SMD −0.79 95% CI −1.28 to −0.31 k=4) and low intensity walking (SMD −0.43 95% CI −0.83 to −0.03 k=2) appeared to reduce improvements in VO_{2peak}. While high intensity training modalities resulted in the greatest increase in VO_{2peak}, the differences compared with moderate intensity training were not significant ($p>0.05$ for all pairwise comparisons). Results of multiple sensitivity analyses, bias assessment and validity assessment can be found in the supplement (eTable 2 and eFigures 2–3).

DISCUSSION

This study used novel methodology to investigate the effect of different potential components of PR on change in VO_{2peak} for people with COPD, demonstrating robust evidence that lower limb aerobic training is the core component for improvements in maximal exercise capacity. Although most moderate to high intensity aerobic exercise components resulted in improvement in VO_{2peak}, the largest numeric improvement was seen with high intensity training modalities. The addition of NIV to aerobic exercise appeared to enhance outcomes but there was limited evidence for the effectiveness of other components in the included trials.

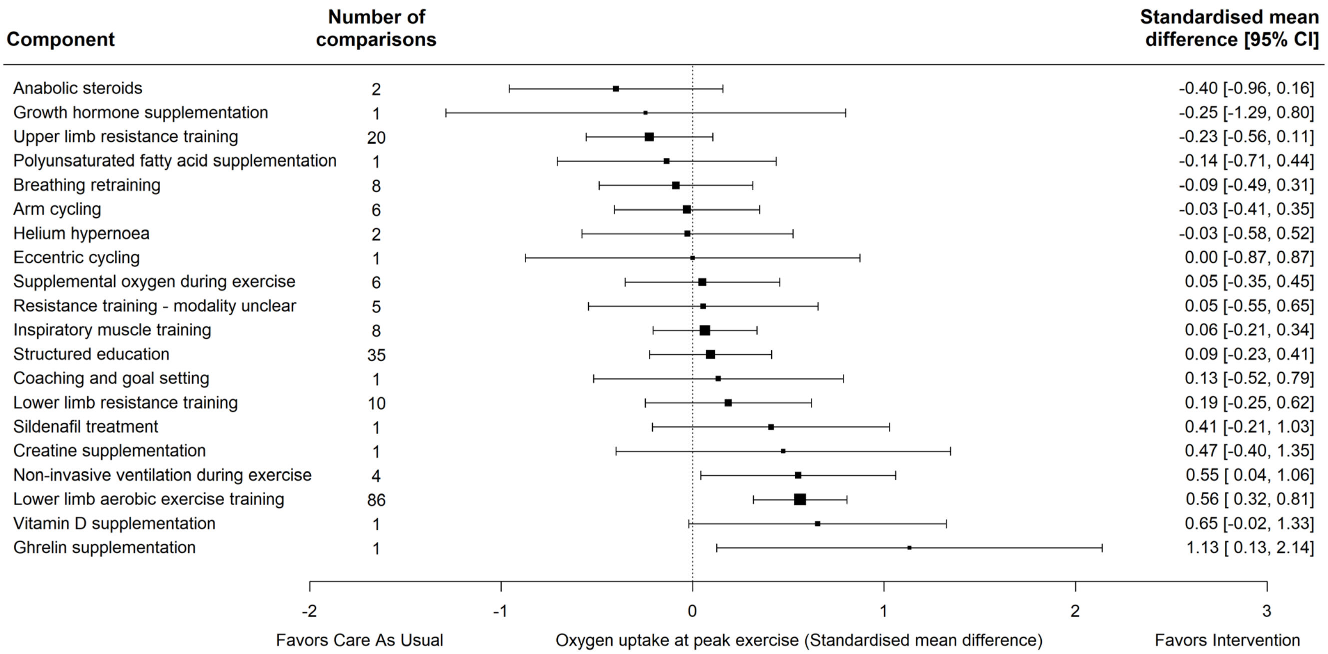

Figure 2 Forest plot showing the individual effect of programme components on oxygen uptake at peak exercise within an additive component network meta-analysis (model 1). The results represent the unique contribution of each individual component when performed as part of a multi-component intervention. All intervention groups included supervised lower limb aerobic training. Reference group is "usual care".

Previous evidence synthesis assessing comparative effectiveness of PR components has been limited to analysis of trials which performed the same head-to-head comparison of different programme designs.[6 10] Our study takes a different approach, allowing multiple programme designs to be compared in a single analysis, providing novel insights into the effectiveness of individual components of complex interventions such as PR. In contrast to previous analyses,[11] our results suggest that high intensity exercise training may be more effective than moderate intensity training for people with COPD.

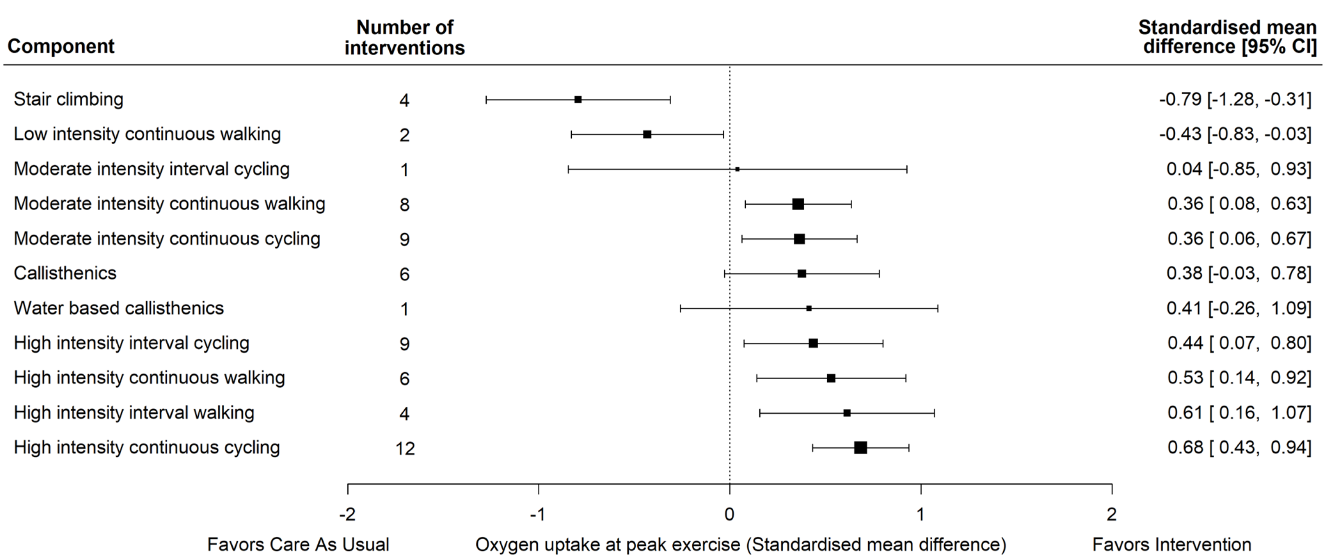

Figure 3 Forest plot showing the individual effect of different components of the aerobic training aspect of the intervention on oxygen uptake at peak exercise within an additive component network meta-analysis (model 2). The results represent the unique contribution of each individual component when performed as part of a multi-component intervention. Reference group is "usual care".

The similarity between interval and continuous training is similar to previous work.[12]

This analysis had several limitations. Only one outcome was investigated and repeating this analysis with a wider range of outcome measures might allow conclusions to be made on the effectiveness of PR on other patient related outcomes. We excluded studies in which the intervention arm performed exercise for less than six sessions in 3 weeks or exercise that was not considered to be aerobically demanding, and we cannot therefore comment on the effect of very low intensity exercise or resistance training in isolation. Our analysis investigated the effects of components and did not consider confounding from factors such as programme duration and frequency, or disease severity. Participants in most studies were not blinded to their intervention introducing the possibility of performance bias however high intensity continuous aerobic training remained effective in those studies at low risk of performance bias. Finally, some of the components included were investigated in a small number of studies and we have therefore avoided making definitive conclusions for components with fewer than three comparisons including the potentially promising effect of ghrelin supplementation alongside exercise training.

In conclusion, lower limb aerobic training is the core effective component of PR to improve VO_{2peak} and there is evidence that NIV during exercise may enhance outcomes. We found limited evidence of the effectiveness of other programme components for additional gains in cardiorespiratory fitness. These results demonstrate the significant heterogeneity that exists in the current delivery of PR programmes and highlights the need for a standardised approach. Although high intensity training may be challenging for patients, our data supports this as the optimal target, and this should be considered in future PR guidelines and standards. Further research is needed to understand the impact of PR components on other patient reported outcomes and to understand the interaction of PR components, training dose and patient demographics.

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Contributors TJCW, MCS and RAE developed the concept with input from TED. TJCW and CDP screened abstracts. TJCW, CDP, TED, LL, SJS, MRL, MCS, RF, AVJ and RAE screened full papers. TJCW and RAE resolved conflicts. AVJ, RT, AVF and TJCW assessed bias. TJCW and LL extracted data. TJCW performed the analysis and drafted the manuscript. All authors revised the final manuscript.

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