THE EXETER ACTIVITY UNLIMITED STATEMENT ON PHYSICAL ACTIVITY AND EXERCISE FOR CYSTIC FIBROSIS: METHODOLOGY AND RESULTS OF AN INTERNATIONAL, MULTIDISCIPLINARY, EVIDENCE-DRIVEN EXPERT CONSENSUS

SUPPLEMENTARY FILE GUIDE:

1. Invitation Document
2. Expression of Interest Form
3. Guideline Document
4. Feedback Document
5. Feedback
6. Meeting Document
7. Evolution of Statements
8. Author Contribution Matrix

PHYSICAL ACTIVITY AND EXERCISE FOR CYSTIC FIBROSIS:

A CONSENSUS STATEMENT

Thank you for your interest in taking part in the consensus group, to help write an expert document, and shape exercise oriented care within cystic fibrosis (CF).

About Us

This work is being coordinated by the 'Youth Active Unlimited' Strategic Research Centre, a UK CF Trust funded project (SRC#006), led by the University of Exeter. More can be read about this research collaboration here: https://www.cysticfibrosis.org.uk/the-work-we-do/research/cf-research-topics/understanding-and-treating-symptoms/src-6-williams-activity

Presently, this group is undertaking two systematic reviews of the literature, focusing on physical and mental health benefits of activity and exercise in CF. The data derived from these two reviews will form the bulk of this consensus document. These reviews have been registered here:
https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=151034
https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=184411

This group has 15 members from around the globe who were co-applicants on the grant and are have agreed to contribute towards this consensus document as a final output of the grant award. This group consists of academics and clinical professionals.

We are looking for a number of experts in activity/exercise for CF who ***are external to this SRC group*** to join us in producing this document. Please do read this document, and all the relevant information below, so that you are clear of the objectives of this consensus group and the forthcoming expectations in terms of workload and anticipated dates. If you have any questions, please do not hesitate to ask us.

Introduction

It is well established that physical activity and exercise are beneficial for people with CF, and therefore such activities are recommended for all people with CF [1,2]. To date, the evidence base that highlights the benefits of activity and exercise is large, but there are many independent facets that must be considered, all of varying levels of quality. This makes the 'true' impact of activity and exercise upon health of patients, and wider management of CF, difficult to accurately describe and interpret.

Therefore, assessment of existing data, and application to people with CF will require expert interpretation and communication. Therefore, a 'consensus document', outlining a series of statements related to exercise management of CF, with ratification by experts in the field of activity, exercise, and CF, is a concise, and evidence-driven way to summarise and publish the wealth of information available.

Similar consensus style documents have been produced within CF, such as for diagnosis [3] and screening [4] of CF, treatment of lung infections [5], non-tuberculous mycobacterium [6] and CFRD [7], inhaled medications [8], and the nutritional management of CF [9,10]. Similarly, consensus documents on the role of activity and exercise for chronic disease have been produced, for example for osteoporosis [11], mental health [12], type 2 diabetes mellitus [13] and ankylosing spondylitis [14].

To date, only one exercise oriented consensus document exists in CF, which concisely summarises evidence in the format of 'questions' and 'recommendations' [15]. However, the CF landscape has drastically changed since this document was produced (e.g., widespread introduction of CFTR modulators), and whilst this is expert-driven, evidence was not graded, and areas that are integral to CF management, such as mental health, are lacking. Therefore, an update is warranted and this project seeks to provide this updated document.

Purpose

Considering the wide range of topics related to activity and exercise, and the variable evidence base for each of them, the purpose of this project is to create an expert group of academic, clinicians, applied practitioners and members of the CF community, and

pool this combined expertise in order to produce an 'Expert Consensus Document' on the role of activity and exercise in CF.

Who are we looking for?

We are looking for ~10 people to join this existing group. You may be an academic, a clinician or an applied practitioner. We are seeking a mixed level of experiences, in order to provide opportunities for early career professionals, under the guidance of established colleagues.

Therefore, if we do not select you to participate, this does not mean we do not value your expertise – we are merely seeking to have a well-rounded group that is not dominated by one subset (e.g., academics).

Finally, we are also seeking the input of ~5 members of the CF community as well. We anticipate these individuals to contribute heavily to the feedback process, and help shape the consensus document, prioritising the views of those with CF.

Anticipated Workload

To produce this consensus document, we are seeking everyone involved to produce a written summary on a particular area related to activity and exercise in CF. For example, such topics may include:

- Physical health benefits of activity and exercise
- Mental health benefits of activity and exercise
- Measurement of activity and exercise
- Contraindications
- Clinical considerations

This list is not exhaustive, but representative at the moment, and we will endeavour to assign you a topic in line with your own interests and expertise.

In particular, we will ask you to:

- Write a ~**500 word summary** on your particular area, having researched this topic and identified pertinent literature of as high a quality as possible,
- **Produce 2-5 'statements'** that arise from this summary,

- **Participate in an anonymous feedback process**, providing your own insights to other summaries that have been written by other members of the group,
- Re-draft your own summary and statements you receive based upon your own feedback, and grade the evidence (this is a very easy to follow process),
- **Participate in a two-day consensus meeting**, currently scheduled for Wednesday June 30th and Thursday July 1st (0900-1500 BST).
    - Within this meeting, you will be asked to discuss your summary and state why you have written what you have written.
    - You will then also participate in an anonymous vote to endorse (or not endorse) the statements that you, and others, have written.
- Following the meeting, you can provide some feedback on the final written document, and then endorse the final version for publication.

Timeline

We expect you to be able to complete the below outlined tasks, within the stated timeframe, outlined on the following pages, to be able to be a member of this consensus group.

If you cannot commit right now, that is absolutely fine. We would much rather know now, and thank you for your interest, than find out months down the line that the timeframe and workload are not feasible.

This may seem like a tight time frame, but please do consider that the workload is not overwhelming, as for many of the topics, the majority of the literature searching has already been completed for the two aforementioned systematic reviews.

This work will all be conducted virtually (email, video calls etc), so there is flexibility in how it is conducted.

Table 1. Proposed timeline and plans/actions.

Date (week commencing)	**Task to be completed**	**How this will be done**
03/05/21	Complete expression of interest form. You will outline your details (name, position etc), and areas of interest/expertise related to activity, exercise, and CF.	Online
10/05/21	Receive invite to participate in consensus group. If successful, you will be allocated a topic to contribute towards, and possibly a co-author to collaborate with. Start researching and summary of evidence.	Email
17/05/21	Research & write summary of evidence. Produce 'consensus points'.	Email
24/05/21	Research & write summary of evidence. Produce 'consensus points'.	Email
31/05/21	First version of summary and consensus points due. Feedback cycle begins.	Email Online
07/06/21	Feedback continues. Re-drafting can begin as feedback is generated.	Online
14/06/21	Feedback closes. Re-draft of summary and consensus points to begin/continue	Online & Email
21/06/21	Grade evidence (details to be confirmed) Final summary & statements due.	Email
28/06/21	Meeting	Virtual Meeting (30/06/ - 01/07)

Table 2. Gannt chart detailing proposed timeline.

w/c	03/05/21	10/05/21	17/05/21	24/05/21	31/05/21	07/06/21	14/06/21	21/06/21	28/06/21	05/07/21	12/07/21
Expression of Interest											
Receipt of Invitation to Group											
Production of Author Bio											
Research of Topic											
Writing of Summary											
Writing of Consensus Points											
Submission of 1st Draft											
Anonymous Feedback Process											
Re-Draft Summary											
Re-Draft Consensus Points											
Grade Evidence											
Submission of Final Version											
Meeting											
Writing of Publications											

Publications

It is anticipated this consensus document will produce two publications. The first will be an executive summary of the statements, approximately two pages long, similar to previous consensus documents that have been published [16]. The second will be a 'full version', explicitly detailing the step-by-step methodology, results, and discussion of the impact of the consensus.

Authorship

All contributors will receive an authorship contribution to both of the aforementioned publications that are planned, provided they fully complete all the work that is outlined within this document.

The order of authorship has yet to be determined, although first and last authorships will be awarded to members of the University of Exeter who are coordinating this process.

Moreover, it is proposed that an authorship matrix, as shown below, will be utilised to highlight individual contributions, in a similar fashion to 'Contribution Statements' that are often advocated for by the IJCME. This matrix will *not* determine authorship order.

Table 3. Example of authorship matrix

	Author					
Contribution	#1	#2	#3	#4	#5	#6
Conceptualisation	■	■				
Project Coordination	■	■				
Content Development	■		■	■	■	■
Participation in Consensus	■		■	■	■	■
Manuscript Development	■		■	■		
Manuscript Review	■		■			
Accountability for Manuscript	■	■	■	■	■	■

Contact

If you have any questions about this process, please do contact us:

Professor Craig Williams: c.a.williams@exeter.ac.uk

Dr Owen Tomlinson: o.w.tomlinson@exeter.ac.uk

Please confirm you expression of interest by completing this form:

https://forms.office.com/r/TN0R1NTGky

REFERENCES

1 Cystic Fibrosis Trust. Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis. 4th Edn. London, UK: 2020.

2 National Institute for Health and Care Excellence (NICE). Cystic fibrosis: diagnosis and management. London, UK: 2017. https://www.nice.org.uk/guidance/ng78

3 Farrell PM, White TB, Ren CL, *et al.* Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. *J Pediatr* 2017;**181**:S4-S15.e1. doi:10.1016/j.jpeds.2016.09.064

4 Castellani C, Macek M, Cassiman J-J, *et al.* Benchmarks for cystic fibrosis carrier screening: a European consensus document. *J Cyst Fibros* 2010;**9**:165–78. doi:10.1016/j.jcf.2010.02.005

5 Doring G, Flume P, Heijerman H, *et al.* Treatment of lung infection in patients with cystic fibrosis: current and future strategies. *J Cyst Fibros* 2012;**11**:461–79. doi:10.1016/j.jcf.2012.10.004

6 Floto RA, Olivier KN, Saiman L, *et al.* US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis: executive summary. *Thorax* 2016;**71**:88–90. doi:10.1136/thoraxjnl-2015-207983

7 Moran A, Pillay K, Becker D, *et al.* ISPAD Clinical Practice Consensus Guidelines 2018: Management of cystic fibrosis-related diabetes in children and adolescents. *Pediatr Diabetes* 2018;**19 Suppl 27**:64–74. doi:10.1111/pedi.12732

8 Heijerman H, Westerman E, Conway S, *et al.* Inhaled medication and inhalation devices for lung disease in patients with cystic fibrosis: A European consensus. *J Cyst Fibros* 2009;**8**:295–315. doi:10.1016/j.jcf.2009.04.005

9 Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. The Consensus Committee. *Am J Clin Nutr* 1992;**55**:108–16. doi:10.1093/ajcn/55.1.108

10 Sinaasappel M, Stern M, Littlewood J, *et al.* Nutrition in patients with cystic fibrosis: a European Consensus. *J Cyst Fibros* 2002;**1**:51–75. doi:10.1016/s1569-1993(02)00032-2

11 National Osteoporosis Society. Strong, Steady and Straight: An Expert Consensus Statement on Physical Activity and Exercise for Osteoporosis. 2019. https://www.bgs.org.uk/sites/default/files/content/attachment/2019-02-20/FINAL%20Consensus%20Statement_Strong%20Steady%20and%20Straight_DEC18.pdf (accessed 27 Apr 2021).

12 Rosenbaum S, Hobson-Powell A, Davison K, *et al.* The Role of Sport, Exercise, and Physical Activity in Closing the Life Expectancy Gap for People with Mental Illness: An International Consensus Statement by Exercise and Sports Science Australia, American College of Sports Medicine, British Association of Sport and

Exercise Science, and Sport and Exercise Science New Zealand. *Transl J Am Coll Sports Med* 2018;**3**:72–3. doi:10.1249/TJX.0000000000000061

13 Sigal RJ, Kenny GP, Wasserman DH, *et al.* Physical activity/exercise and type 2 diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care* 2006;**29**:1433–8. doi:10.2337/dc06-9910

14 Millner JR, Barron JS, Beinke KM, *et al.* Exercise for ankylosing spondylitis: An evidence-based consensus statement. *Semin Arthritis Rheum* 2016;**45**:411–27. doi:10.1016/j.semarthrit.2015.08.003

15 Swisher AK, Hebestreit H, Mejia-Downs A, *et al.* Exercise and habitual physical activity for people with cystic fibrosis: Expert consensus, evidence-based guide for advising patients. *Cardiopulm Phys Ther J* 2015;**26**:85–98. doi:10.1097/cpt.0000000000000016

16 Bangsbo J, Krustrup P, Duda J, *et al.* The Copenhagen Consensus Conference 2016: children, youth, and physical activity in schools and during leisure time. *Br J Sports Med* Published Online First: 27 June 2016. doi:10.1136/bjsports-2016-096325

CF Consensus Group - Expression of Interest

Thank you for your interest in joining this consensus group. Please make sure you have read the below 'Invitation Document' and filled out all the questions.

Deadline = 09/05/2021 (1800 BST)

1. Title/Pronoun & Name

2. Institution

3. Email address

4. Are you:

- ◯ Academic (Lecturer, Researcher, Doctoral Student etc)
- ◯ Clinical Professional (Doctor, Physiotherapist, Exercise technician etc)
- ◯ Someone with CF

5. Would you consider yourself an 'Early Career' professional/researcher?

- ◯ Yes
- ◯ No

6. How did you hear about this consensus group?

- ◯ ECFS Exercise Working Group
- ◯ ACPCF
- ◯ CF & Exercise Network
- ◯ CF Trust
- ◯ Other

7. Briefly, what is your motivation for wanting to join this group?

8. Briefly, what is your area of expertise in relation to activity, exercise and CF?

9. Please confirm you have: a) read the Invitation Document, b) are able and willing to commit to the timeline and anticipated workload, and c) can attend the consensus meeting scheduled for June 30th & July 1st 2021.

- ◯ Yes
- ◯ No

PHYSICAL ACTIVITY AND EXERCISE FOR CYSTIC FIBROSIS:

A CONSENSUS STATEMENT

Thank you for your involvement within this group. We look forward to working with you to produce this expert consensus document on the role of both physical activity and exercise in CF management for both adults and children.

1. About Us

This work is being coordinated by the 'Youth Active Unlimited' Strategic Research Centre, a UK CF Trust funded project (SRC#006), led by the University of Exeter. More can be read about this research collaboration here: https://www.cysticfibrosis.org.uk/the-work-we-do/research/cf-research-topics/understanding-and-treating-symptoms/src-6-williams-activity

2. Why a consensus document?

As this long-term project comes to a close, we are seeking to pool many of our findings, and link this to the existing evidence base. Expert-driven consensus will utilise the wider academic and clinical experience of those working in CF to synthesise (in an easy to understand way) and describe the role of activity and exercise for people with CF.

There are presently systematic reviews, and other expert statements in existence. However, these are very focused in their nature, selecting one singular topic to discuss in detail. Activity and exercise requires multi-disciplinary action in actual practice, and therefore this consensus will take a holistic approach to this document, simultaneously considering all aspects of activity and exercise in a single document.

3. Why we have we invited you?

We have invited you because you are an expert in the field of activity and/or exercise in CF. This may be from an academic background with research experience, or a

clinical background with extensive applied experience, or both. We want a wide-range of voices to be involved, to ensure multiple opinions and areas of interest are covered.

Following our 'expression of interest', we have narrowed down this list, and we now have a mix of established and early-career individuals, from around the globe. This group has a range of academic and applied experience in all aspects of exercise for CF – creating a very well rounded team.

4. What are the next steps?

You will have been partnered with one other person to write a summary of the evidence in a particular area of CF and activity/exercise, alongside a singular position statement that concisely synthesise this evidence. As per the invitation document, there are a series of steps for us all to complete, and these are now outlined in detail below.

4.1. 500 word summary – 1st draft due Wednesday 2nd June

We are asking you research, and write approximately 500 words on your particular topic area that you have been assigned. This is a similar length to an academic abstract, so will need to be concise.

- This 500 words is an upper guideline, and we do not expect you to write beyond this, as all writing will still be required to fit into a manuscript alongside all the other topics. We want to make this document as easy-to-read as possible, and a lower word limit will prevent each sub-theme from being overwhelmed with information.
- There are five 'themes' that will contribute towards this final document, with sub-themes below these themes. Each pair is contributing towards one of these sub-themes.
- These themes, and sub-themes, have been identified and chosen based upon the topics that exist within current guidelines that are used by healthcare professionals within CF care (e.g., CF Trust Physiotherapy guidelines, NICE guidelines for CF, CF Foundation Care guidelines) and from the James Lind priority setting partnership. The final topics are listed below.
- Depending on the sub-theme you have been assigned, you may have to perform some literature searching yourself. If this is the case, then we would

ideally like to see synthesis of higher-quality evidence (e.g., meta-analyses, systematic reviews) if possible, but if such evidence is not available, then please summarise what information is available (e.g., cohort studies, case control etc.)

- If you are assigned a topic that is currently part of our systematic review process, you will be provided with a summary of the PRISMA process, data, and papers that can be cited.
- Please ensure any references use a numbered format (e.g., BMJ, Vancouver) as opposed to a style that requires insertion of authors names. Please ensure all reference lists have as much detail as possible so that we can easily compile all references in to a 'master list'.

Table 1. Final themes for consensus document

	Theme	**Sub-theme**
1	Rationale for activity & exercise	Patient oriented outcomes (e.g. mortality, transplant risk) System oriented outcomes (e.g. economic benefits, bed-days)
2	Health benefits of activity & Exercise	Lung Health Cardiovascular Health Musculoskeletal Health Fitness & Strength Other Physical Health Benefits Mental Health Quality of Life
3	Measurement of PA & Exercise	Measurement of physical activity Measurement of exercise
4	Prescription of PA &Exercise	Optimal Training Modes & Styles Improving Adherence Staff/Service Requirements Telehealth
5	Clinical Considerations	Airway Clearance Modulators Risks of activity & exercise Nutrition & Hydration

4.2. Production of statements – 1st draft due Wednesday 2nd June

These summary statements will, where possible, succinctly condense these 500-word abstracts into a singular point. For example, the following statements are from the 2016 Copenhagen Consensus on physical activity for young people (Bangsbo J et al., 2016, Br J Sports Med: 50, 1177-1178):

- *Cardiorespiratory and muscular fitness levels in children and youth are strong predictors of future cardiometabolic disease, such as coronary artery disease and diabetes mellitus.*
- *Vigorous exercise has a marked favourable impact on cardiometabolic fitness and other cardiovascular risk factors in children and youth.*
- *Frequent moderate-intensity and, to a lesser extent, low-intensity exercise improves cardiometabolic fitness in children and youth.*

As you see, these statements do not contain explicit data, but take a broad and holistic approach to the interpretation of the data. Given that the purpose of this consensus document is to create an easy-to-read/disseminate summary of evidence, these statements do not need to be overwhelming, but they do need to be accurate. Do not say exercise and activity are beneficial if the evidence does not wholly support this. You will need to consider the language you are using when constructing these statements, and we are therefore asking each pairing to produce a singular position statement that summarises their evidence. In describing any relationships or associations then please try to be as explicit as the evidence supports.

As a fictional example, this is a possible statement that could be written.

"Participation in exercise and activity can offset declines in lung function in CF"

As you see, this statement uses the word *"can"* to act as a qualifying word, not "does" or "definitely", thus reflecting the confidence with which the data can be summarised. It is this wording that we will, as a group, seek to get as explicitly accurate as possible through our feedback and discussions. Following feedback and discussion, this statement will be endorsed via a vote after the final meeting – thus creating the *consensus* behind the *expert statement*.

4.3. ***Participation in feedback process – starts Thursday 3rd June/ends Friday 11th June***

This will be completed online, using a platform called Padlet (https://en-gb.padlet.com/). This platform allows anonymous feedback to be delivered via 'sticky notes' (similar to a PDF) on each summary and statements. This method has been

chosen as it is a) anonymous, and b) avoid excessive modification to text that is often seen when a word document is extensively edited by multiple people. The full details for the feedback process will be circulated in due course.

4.4. Re-drafting – Final draft due Friday 25th June

Following on from the feedback process (or during if you're keen), you will be asked to make any necessary changes (e.g., if you have missed some pertinent literature) and re-draft your own summary and statements. The statements will not be the *final* statements that will be used (although will be very close to final versions), as this will be discussed and finalised within the consensus meeting; however, this process ensures that enough feedback has occurred that a consensus can be reached on the final phrasing of statements during the meeting (and we do not spend the whole meeting editing statements extensively).

4.5. Consensus Meeting – Wednesday 30th June & Thursday 1st July

This meeting, as already stated, is scheduled for Wednesday June 30th and Thursday July 1st (0900-1500 BST). This will be hosted online (likely via Zoom or MS Teams). If your time-zone is not conducive to attending the entire meeting, that is absolutely fine. Please don't be awake in the middle of the night if you don't have to be. Just attend what you can.

Within this meeting, you will be asked to discuss your summary, ideally with some slides, and state why you have written what you have written and how you have taken account of feedback. Each pair will present for around 10 minutes, and then there will be 20 minutes of follow up discussion amongst the group to critique and modify the wording of the final statement that will be used.

As each pair will 'have the floor' for around 30 minutes in total, we anticipate that the whole consensus meeting will take six hours per day. This will include time for coffee breaks and lunch. Your time-slot for presentation will be adapted to your availability if you or your partner are in a time-zone that necessitates an early/late slot.

Following the presentation and discussion of each statement at the meeting, these will be collated and a survey created. This will be an anonymous survey sent around at

the end of the meeting, and ask you for each statement, *"Do you endorse this statement?"*. If a majority of people agree with the statement, then it will be accepted as a group endorsement and included in the final consensus statement.

Details and a running order of the consensus meeting itself will be circulated in due course.

4.6. Publication

Following the meeting, you can provide some feedback on the final written document, and then endorse the final version for publication, where you will be invited as a co-author. We will not be inviting extensive modification at this stage (that is what the meeting is for). However, we will take feedback on obvious spelling mistakes, names/institutional corrections etc.

5. Timeline

As per the original invitation document, the timeline for this process is presented below.

6. Contact

If you have any questions about this process, please do contact us:

Professor Craig Williams: c.a.williams@exeter.ac.uk

Dr Owen Tomlinson: o.w.tomlinson@exeter.ac.uk

Table 1. Proposed timeline and plans/actions.

Date (week commencing)	**Task to be completed**	**How this will be done**
03/05/21	Complete expression of interest form. You will outline your details (name, position etc), and areas of interest/expertise related to activity, exercise, and CF.	Online
10/05/21	Receive invite to participate in consensus group. If successful, you will be allocated a topic to contribute towards, and possibly a co-author to collaborate with. Start researching and summary of evidence.	Email
17/05/21	Research & write summary of evidence. Produce 'consensus points'.	Email
24/05/21	Research & write summary of evidence. Produce 'consensus points'.	Email
31/05/21	First version of summary and consensus points due. Feedback cycle begins.	Email Online
07/06/21	Feedback continues. Re-drafting can begin as feedback is generated.	Online
14/06/21	Feedback closes. Re-draft of summary and consensus points to begin/continue	Online & Email
21/06/21	Grade evidence (details to be confirmed) Final summary & statements due.	Email
28/06/21	Meeting	Virtual Meeting (30/06/ - 01/07)

Table 2. Gannt chart detailing proposed timeline.

w/c	03/05/21	10/05/21	17/05/21	24/05/21	31/05/21	07/06/21	14/06/21	21/06/21	28/06/21	05/07/21	12/07/21
Expression of Interest											
Receipt of Invitation to Group											
Production of Author Bio											
Research of Topic											
Writing of Summary											
Writing of Consensus Statement											
Submission of 1st Draft											
Anonymous Feedback Process											
Re-Draft Summary											
Re-Draft Consensus Points											
Submission of Final Version											
Meeting											
Writing of Publications											

PHYSICAL ACTIVITY AND EXERCISE FOR CYSTIC FIBROSIS:

A CONSENSUS STATEMENT

This document outlines the process and timeline for the feedback process. The purpose of this is to provide everyone with an opportunity to a) receive feedback on your 500-word summaries and provisional position statement, and b) provide your own expert opinion on the other topics and summaries that have been written by other people.

Feedback Process

As noted previously in the 'Guideline Document', the feedback process will be completed online, using a platform called 'padlet' (https://en-gb.padlet.com/).

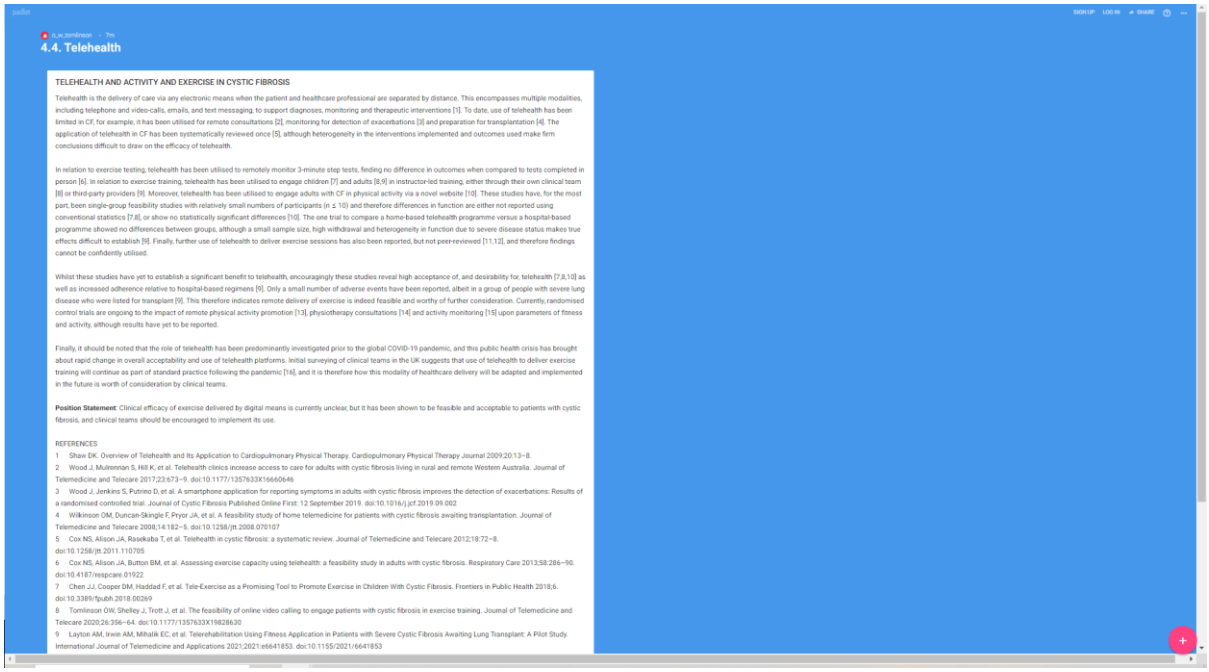
This platform allows anonymous feedback to be delivered via 'sticky notes' (similar to a PDF) on each summary and statements. This method has been chosen as it is a) anonymous, and b) avoid excessive modification to text that is often seen when a word document is extensively edited by multiple people. You do not need a 'padlet' profile to sign up, and can provide feedback in a wholly anonymous manner.

Whilst this process is anonymous, to allow people to have more confidence in their own voice and opinion, we do ask people stick to two simple rules:

1. **Please be polite and considerate in your feedback.** There will inevitably be disagreement on some things, this is why we have a wide ranging panel to ensure all voices and experiences are heard. But be kind and respectful when providing feedback, particularly if you disagree with something.
2. **Please, where possible, be constructive.** Let someone know how they can change something and why (if you can). We have a large number of early career researchers and professionals in this group, and constructive feedback is always preferential.

How to provide Feedback

When you click on the link for each topic, you will see a page similar to the image below, whereby the 500 word summary, position statement, and associated references will be listed.

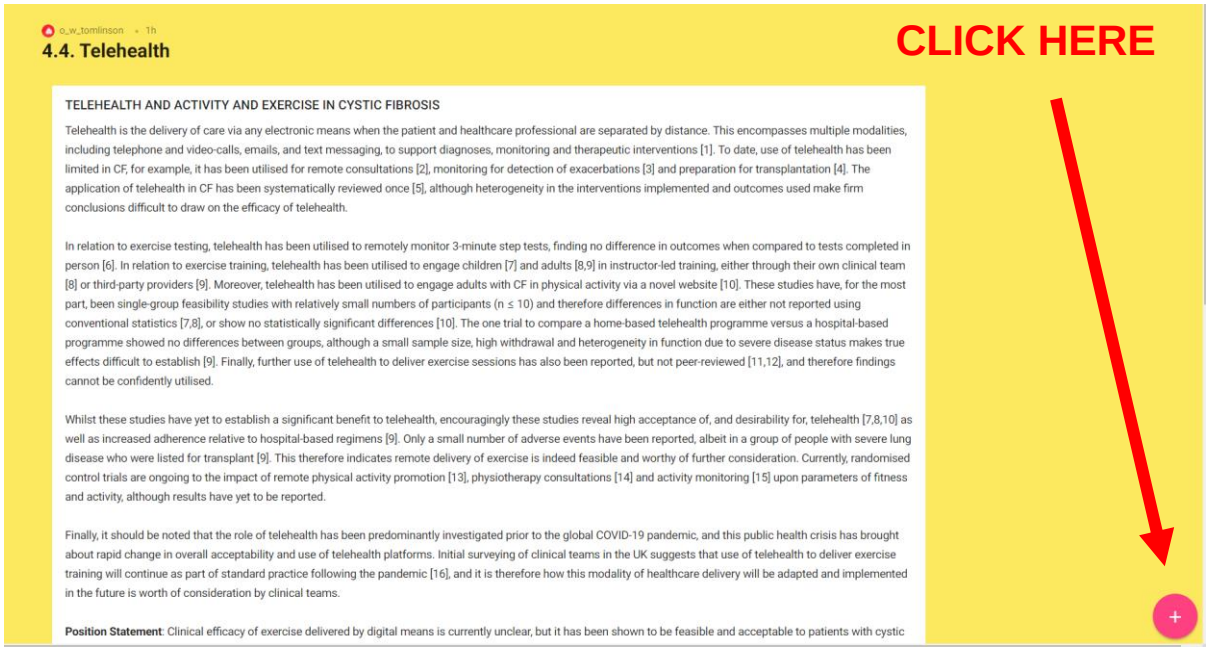


Please read the summaries, and the provisional position statements, and then provide any feedback that you see fit.

We do acknowledge that we have a large number of sub-themes; 19 in total. Therefore, we do not expect everyone to provide feedback on every topic (although you can if you like!). Instead, please provide feedback on the topics you feel you are best placed to do so on. This may be because these sub-themes align with your own research and/or clinical interests, or because it is an area that of interest otherwise. To ensure that each sub-theme receives appropriate feedback, **please do try to review at least three sub-themes each.** If everyone takes this approach, then we should end up with an adequate amount of feedback being provided.

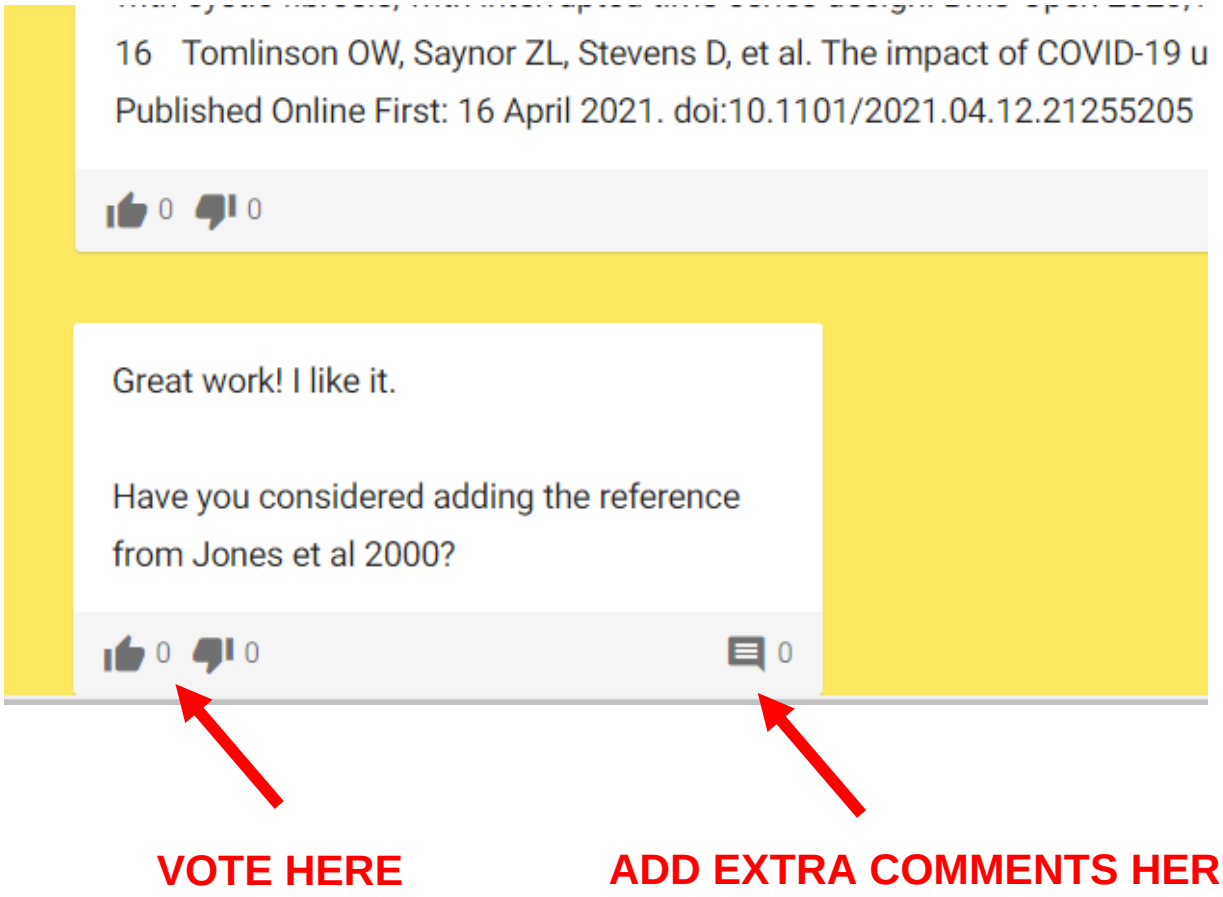
Even if you have nothing to explicitly add as feedback, even saying “this is great, and I agree with your opinion” still counts as viable (and no doubt, confidence boosting) feedback.

To provide feedback, first click the pink '+' button in the bottom right of the screen.



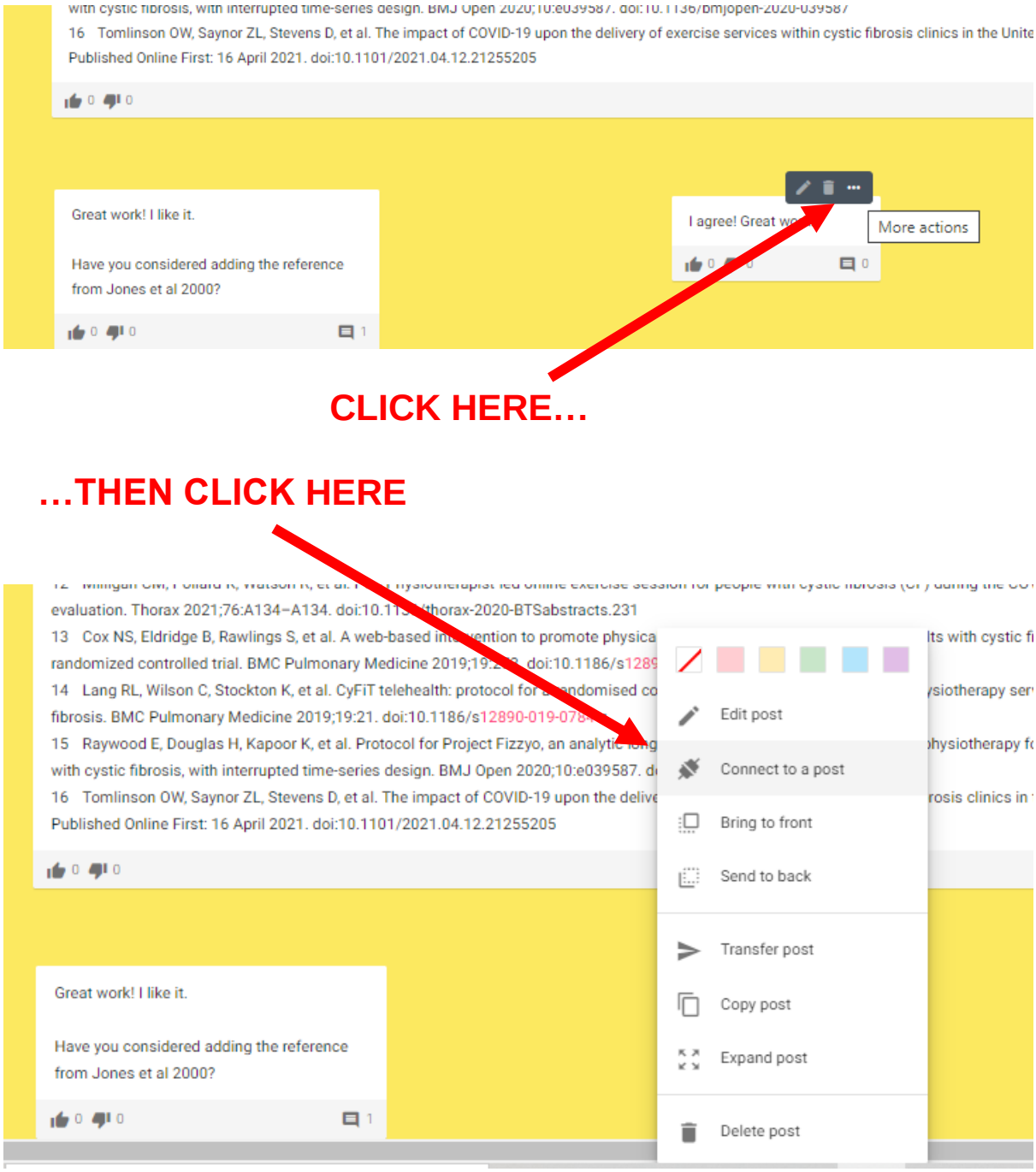
This will then bring up a dialogue box, as shown below. You can then write in the box (where it says 'write something') to provide any comments you have. NB. There is a 'title' function for each box, but you do not need to fill this out.

Once you have provided feedback, you can then drag the box to any where on the screen. Following this, people can ‘upvote’ and ‘downvote’ your comments if they agree/disagree, as well as being able to provide further comments.



Finally, you also have the ability to ‘link’ comments. If you have written something and want to associate it to another post, you can use the ‘More Actions’ function (the three dots that appear when you hover over the comment box) to ‘Connect to a Post’.

Click the ‘Connect to a Post’ function, and then you can choose which post to ‘connect’ to. This will then produce an arrow between the boxes to show they are ‘connected’.



All comments are automatically saved, so when you leave the page, they will be retained for the authors to see.

Please note, the summaries, and their position statements are ‘locked’, so they cannot be modified themselves, only commented upon. Therefore, if you have a suggestion for something to be re-written, you will have to explicitly state in your feedback comment where this suggested change should be.

Where to find the feedback

The themes of this consensus, and sub-themes, have been circulated previously and each pair has been working on a particular sub-theme over the past weeks. Each topic will have its own padlet 'page'. The links to these Padlet pages will be circulated on Monday 7th June.

Timeline

The feedback process will open on Monday 7th June. It will close on Sunday 13th June. Thereafter, as of Monday 14th June, we will request authors view their feedback and make any necessary changes as below.

Re-drafting

Following on from the feedback process, you will be asked to make any necessary changes (e.g., if you have missed some pertinent literature) and re-draft your own summary and statements.

This will not be the final statements that will be used, as this will be discussed and finalised within the consensus meeting; however, this process ensures that enough feedback has occurred that a consensus can be reached on the final phrasing of statements during the meeting (and we do not spend the whole meeting editing statements extensively).

Final copies will be due on Friday 25th June at 1800 BST.

Contact

If you have any questions about this process, please do contact us:

Professor Craig Williams: c.a.williams@exeter.ac.uk

Dr Owen Tomlinson: o.w.tomlinson@exeter.ac.uk

o_w_tomlinson + 11 · 2m

1.1 Patient Oriented Rationale for Activity & Exercise

PATIENT ORIENTED RATIONALE

Exercise capacity can predict morbidity and mortality in CF, independent of lung function. Specifically, people with CF that exhibited a higher VO_2peak had a longer life expectancy, whereas a greater severity of disease and mortality was associated with those with a lower exercise capacity [1]. In addition, conducting exercise testing can provide additional prognostic value for patients who need lung transplantation[2]. Accordingly, over the past 3 decades, exercise has been recommended in CF. In addition to the improvements in exercise capacity, people with CF can experience many other benefits of engaging in exercise/physical activity. In fact, there is substantial data to demonstrate that both children and adults with CF who are physically active report having a better quality of life compared to those patients who are sedentary. Higher health related quality of life is significantly related to both reported physical activity[3] and daily accelerometer counts[4]. In addition, patients have reported higher scores in quality of life when engaging in >30min of moderate-vigorous physical activity[5] or at least 90 minutes of moderate to strenuous exercise per week[6].

Due to the positive relationships between physical activity and quality of life, much interest has focused on identify the most beneficial mode, duration, and intensity of exercise for people with CF. As little as 4 exercise counseling sessions in children with CF demonstrated a noticeable increase in the physical well-being dimension[7]. In addition, exercise in children hospitalized for an acute exacerbation was able to improve quality of well-being 1 month after discharge compared to those children who did not exercise during hospitalization[8]. When compared to no training at all, 12 weeks of anaerobic training, 30-45 minutes per day, 2 days a week was shown to improve the physical functioning domain of the cystic fibrosis questionnaire revised (CFQ-R) in children with CF[9]. However, aerobic training appears to be more beneficial at improving quality of life in children with CF, compared with resistance training alone[10]. Interestingly, both video game training[11] 30-60 minutes per day, 5 days per week for 6 weeks and yoga therapy[12], twice per week for 8 weeks can improve the respiratory domain of the CFQ-R in people with CF. In addition, supervised exercise conditioning for 3 months was able to improve subjective health perception and the improvements were still maintained at the 2 year follow-up. [13] Consistent with this, 3 years of home exercise was able to maintain quality of life in patients with CF [14].

Position Statements:

1. Although resistance training can be beneficial compared to no training, aerobic training at least 150 minutes per week is the most effective at improving overall quality of life in CF.
2. Physical activity and fitness have positive associations with increased longevity and reduced morbidly for people with CF.

REFERENCES

1. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The Prognostic Value of Exercise Testing in Patients with Cystic Fibrosis. *New England Journal of Medicine*. 1992;327(25):1785-1788. doi:10.1056/nejm199212173272504
2. Hebestreit H, Hulzebos EHJ, Schneiderman JE, et al. Cardiopulmonary Exercise Testing Provides Additional Prognostic Information in Cystic Fibrosis. *Am J Respir Crit Care Med*. Apr 15 2019;199(8):987-995. doi:10.1164/rccm.201806-1110OC
3. Hebestreit H, Schmid K, Kieser S, et al. Quality of life is associated with physical activity and fitness in cystic fibrosis. *BMC Pulmonary Medicine*. 2014;14(1):26. doi:10.1186/1471-2466-14-26
4. Dwyer TJ, Elkins MR, Bye PT. The role of exercise in maintaining health in cystic fibrosis. *Curr Opin Pulm Med*. Nov 2011;17(6):455-60. doi:10.1097/MCP.0b013e32834b6af4
5. Cox NS, Alison JA, Button BM, Wilson JW, Morton JM, Holland AE. Physical activity participation by adults with cystic fibrosis: An observational study. *Respirology*. 2016;21(3):511-518. doi:10.1111/resp.12719
6. Dwyer TJ, Griffin B, McKeough ZJ, Bye PT, Alison JA. Differences in quality of life, lung function and hospitalisation rates for adults with cystic fibrosis, according to exercise participation. *Journal of Cystic Fibrosis*. 2010;9:S69. doi:10.1016/s1569-1993(10)60268-8
7. Moola FJ, Garcia E, Huynh E, et al. Physical Activity Counseling for Children With Cystic Fibrosis. *Respiratory Care*. 2017;62(11):1466-1473. doi:10.4187/respcare.05009
8. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. *Pediatric Pulmonology*. 2002;33(3):194-200. doi:10.1002/ppul.10015
9. Klijn PH, Oudshoorn A, van der Ent CK, van der Net J, Kimpen JL, Helders PJ. Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. *Chest*. Apr 2004;125(4):1299-305. doi:10.1378/chest.125.4.1299
10. Wilkes DL, Schneiderman JE, Nguyen T, et al. Exercise and physical activity in children with cystic fibrosis. *Paediatr Respir Rev*. Sep 2009;10(3):105-9. doi:10.1016/j.prrv.2009.04.001
11. Del Corral T, Cebrià I Iranzo MÀ, López-De-Uralde-Villanueva I, Martínez-Alejos R, Blanco I, Vilaró J. Effectiveness of a Home-Based Active Video Game Programme in Young Cystic Fibrosis Patients. *Respiration*. 2018;95(2):87-97. doi:10.1159/000481264
12. Ruddy J, Emerson J, McNamara S, et al. Yoga as a Therapy for Adolescents and Young Adults with Cystic Fibrosis: A Pilot Study. *Global Advances in Health and Medicine*. 2015;4(6):32-36. doi:10.7453/gahmj.2015.061
13. Hebestreit H, Kieser S, Junge S, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. *European Respiratory Journal*. 2010;35(3):578-583. doi:10.1183/09031936.00062409
14. Schneiderman-Walker J, Pollock SL, Corey M, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. *J Pediatr*. Mar 2000;136(3):304-10. doi:10.1067/mpd.2000.103408.

0 0

Will need to ensure terms are defined.

0 0 1

Evidence for improved exercise capacity? The 'fitness' section is slightly more cautious.

0 0

---

introduction

nice section
maybe have a look to the use of "sedentary" line 7. Do you want to refer to sedentary behavior or to lack of physical activity (which is not the same thing and which is not measured identically).

2 0

Other outcomes to consider

Does increased exercise impact treatment burden

e.g.

Can exercise replace chest physiotherapy for airway clearance

By doing exercise as a replacement for physio can we reduce treatment burden

See works by Nathan Ward and Anne Holland as well as proof of concept studies by Tiffany Dwyer

0 0

In places some of the statements made are similar, this section could possibly be more concise.

0 0

Statement 1

This is very strong - is there strong evidence to support?

2 0

May need to liaise with people completing other exercise training sections to ensure there is minimal repetition around mode/dose of exercise training

0 0

Thanks for this clear summary.
We may need to consider how the details here relating to quality of life reports correspond with the quality of life 'section (2.7)'? and also whether one or the other section needs a slightly different focus?

5 0

Identity

Would be good to clarify the focus of this section, as fitness and QoL are covered elsewhere.

5 0 1

I think statement 2 is supported by the above points. Statement 1 I have some confidence in but the evidence is not as clear as number 2.

0 0

Position Statement

Should just be one sentence

0 0 1

There seems to be some overlap with the QOL section summary (2.7) ....was this the intention for this summary?

3 0 1

Agree with the previous points about overlap with QoL. Perhaps you could say that exercise/activity has health benefits but that these will be discussed in detail in the later sections?

I think the 2nd position statement sums this area up well and could be more of the focus of this section?

0 0

Referencing Style

No guidelines were given for overview consistency or referencing style. Need to ensure consistency throughout reviews.

0 0 1

Is the fitness data more supportive of this than physical activity, especially for longevity?

2 0

Numbers less than 10 should be written in full.

0 0

In the second position statement the word 'morbidly' is used ... should this be morbidity?

2 0

o_w_tomlinson + 10 · 1mo

1.2 Health System Rationales for Activity & Exercise

HEALTH SYSTEM ORIENTED OUTCOMES

With improving health outcomes and the prospects of further advances with genetic modifiers, people with cystic fibrosis (CF) will increasingly become subject to the same health concerns as in the general population. The World Health Organisation (WHO) reminds us that exercise has significant physical and psychological health benefits but reports that 80% of the world's population is not active enough [1]. There is a growing recognition that physical inactivity has a significant global economic impact. In the United States (US) alone, it was estimated that there were more than 500,000 premature deaths and health care costs in excess of $100 billion annually were caused by physical inactivity and obesity [2]. The RAND organisation estimated that increasing activity levels across the population could boost global GDP by up to $726 billion (US) dollars by 2050 [3].

To date, there is no evidence to suggest a causal relationship between physical activity and exercise with health system-oriented outcomes such as hospitalisations or antibiotic use in people with CF. Previous research in chronic respiratory disease, such as people with chronic obstructive pulmonary disease (COPD) undergoing pulmonary rehabilitation (including aerobic and strength training) has been shown to reduce subsequent hospital admissions, bed days and decrease health-care costs [4, 5].

Respiratory exacerbations requiring hospital admission continue to be one of the hallmarks of CF, and the annual prevalence of respiratory exacerbations increases with age [6]. Hospitalisations are the primary reason for healthcare costs in CF [7]. However, there is limited reporting of respiratory exacerbations as an outcome measure in physical activity and exercise interventions in this cohort. Only one study in a Cochrane review of physical training interventions in CF reported on hospitalisations [8]. This study evaluated the effect of a three-year aerobic training program and found no significant difference between the mean number of hospital days or the mean number of hospitalisations at 1, 2 and 3 year follow ups [8, 9]. However, a 3-year longitudinal study found a significant association between greater aerobic fitness and lower risk of hospitalisation in 77 children with mild-moderate CF [10]. Furthermore, a 1-year supervised, outpatient exercise intervention resulted in a significant reduction in the use of intravenous antibiotics when compared to the previous year and reported significant cost savings as a result. Future research should further evaluate the impact of exercise interventions on health system outcomes such exacerbations, hospitalisations, and antibiotic use.

Position Statement: The effect of activity and exercise on health system outcomes in CF requires further investigation. There is no evidence to date to suggest a causal relationship between exercise and hospitalisations. Future intervention and longitudinal studies should consider further exploring the impact of exercise on health system outcomes such as exacerbations, hospitalisations, and antibiotic use.

REFERENCES

1. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British Journal of Sports Medicine 2020;54(24):1451-1462.
2. Myers J. The health benefits and economics of physical activity. Current sports medicine reports 2008;7(6):314-316.
3. Hafner M, Yerushalmi E, Phillips WD, Pollard J, Deshpande A, Whitmore M, et al. The economic benefits of a more physically active population: an international analysis. 2019.
4. Spruit MA, Singh SJ, Garvey C, ZuWallack R, Nici L, Rochester C, et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. American journal of respiratory and critical care medicine 2013;188(8):e13-e64.
5. Puhan MA, Gimeno-Santos E, Cates CJ, Troosters T. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. Cochrane database of systematic reviews 2016(12).
6. Cystic Fibrosis Foundation. Patient Registry: Annual Data Report
7. Van Gool K, Norman R, Delatycki MB, Hall J, Massie J. Understanding the costs of care for cystic fibrosis: an analysis by age and health state. Value in health 2013;16(2):345-355.
8. Radtke T, Nevitt SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. Cochrane Database of Systematic Reviews 2017(11).
9. Schneiderman-Walker J, Pollock SL, Corey M, Wilkes DD, Canny GJ, Pedder L, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. The Journal of pediatrics 2000;136(3):304-310.
10. Pérez M, Groeneveld IF, Santana-Sosa E, Fiuza-Luces C, Gonzalez-Saiz L, Villa-Asensi JR, et al. Aerobic fitness is associated with lower risk of hospitalization in children with cystic fibrosis. Pediatric pulmonology 2014;49(7):641-649.

0 0 0

This is a clear and well written section

0 0 0

if there is space, might want to comment on the estimated cost of hospitalization for an exacerbation

2 0 0

I like this, agree with the points made

3 0 0

this section is excellent, very well-written and clear

2 0 0

Thanks. This is really clear. I like the inclusion of 'future directions' in the position statement.

1 0 0

Good job

Nice abstract and the position statement is clear.

3 0 0

The following article may also be of interest if you haven't already come across it - Cox NS, Alison JA, Button BM, Wilson JW, Morton JM, Holland AE. Physical activity participation by adults with cystic fibrosis: an observational study. Respirology 2016;21:511–8. https://doi.org/10.1111/resp.12719.

0 0 0

might be worth including the Ledger et al 2013 reference which refers to IV use and admissions

- DOI: 10.1016/j.jcf.2013.01.003

and Urquhart et al 2012

- DOI: 10.1002/ppul.22587

which looked at IV days also

3 0 0

This may also be a useful study, looking at fitness and antibiotic usage in children: https://pubmed.ncbi.nlm.nih.gov/28965267/

0 0 0

Where you state that a one-year supervised training intervention resulted in a reduction of IVAB - do you have a reference for that?

0 0 0

Exercise and IV days

Some evidence that exercise may impact IV use

Out-patient exercise and Physio intervention studies

Black R, et al. *Pediatr Pulmonol* 2009; **44 (S10):** 391-392.

Ledger SJ, et al. *J Cyst Fibros* 2013;**12:**766-772.

Urquhart D et al. *Pediatr Pulmonol* 2012;**47:** 1235-1241.
I think this is alluded to in text but not referenced

0 0 0

Craig's comment: suggest we delete the first sentence of the statement and focus on a direct statement, as all the statement would have this first sentence in them. Is there anything positive we can frame re exercise and the systems outcomes e.g. "Engagement in PA and exercise has the potential to positively influence hospitalisations, exacerbations and antibotic use." I know this is not necessarily supported by your evidence above, so is not quite correct a statement, but hopefully you understand my thinking.

2 0 0

o_w_tomlinson + 11 · 1mo

2.1 Lung Health

EFFECT OF EXERCISE ON LUNG HEALTH IN CYSTIC FIBROSIS

There have been several studies examining the relationship between Exercise in Lung Health, primarily looking at lung function as a primary study outcome. While it is well recognised that exercise is beneficial the strength of the evidence to support a statement of preservation of lung health is challenging.

Three Systematic Reviews concluded an unclear effects of exercise on Forced Expiratory volume in 1 second (FEV1), due to a wide range of studies design, heterogeneous exercise training modalities and duration of intervention. (1,2,3)

A study examined the longitudinal relationship between physical activity and lung health in a large cohort of 212 children. There was a significant correlation between the rates of change of activity level and change in FEV1 decline, indicating that an increasing activity is associated with a slower rate of decline (p<= 0.007) and thus the possibility of affecting survival. (4)

Studies that evaluated the longer time effect of exercise concluded that exercise slows the decline in lung function. (5, 6, 7) A study with 2 years follow up display, control group demonstrated a greater mean annual rate in percent of predicted forced vital capacity (FVC) compared to exercise group (p=0,02) with a similar trend for FEV1 (p=0,07) (5) Another study showed a better preserved FEV1 at 1 year with exercise intervention, small improvements in FVC in the active group but significant decline in FVC in the inactive group. (6)

A retrospective study including 1038 twins or siblings showed that those reporting exercise had a high baseline FEV1 % predicted than those that did not (p=0.001). Also, that exercising adults with CF would experience a smaller decline in FEV1 compared to exercising children, suggesting adults received more benefit. Finally, that subjects with a lower FEV1 who perform any exercise may benefit disproportionately better than those with a better lung function in terms of FEV1 decline. (7)

Studies have evaluated the effect of different intervention of exercise and dose response in lung function. (8, 9) A study looked at a single bout of Maximal exercise displaying a significant increase in FVC (p< 0.002) and FEV1 (p<0.002). Pre and post Lung Clearance Index (LCI) was examined displaying a significant reduction (p<0.05). This study suggested that higher intensity exercise may contribute to greater improvements in pulmonary function. (8) Another study examined the potential difference between Strength and Aerobic training compared to controls. This RCT showed a significant increase in FEV1 in both training groups compared to controls (p<0.001) but the effects had been lost by 18months post exercise program. (9)

What can be concluded is that there is strong evidence of a reduction in the rate of decline in FEV1 with exercise. With less confidence we can report that this improvement is dose dependant, with those exercising at higher intensity receiving most benefit. The type or exercise performed is not important, as long as it is performed at a high intensity for training effect.

Position Statement: Exercise can reduce the rate of decline in FEV1 in cystic fibrosis.

REFERENCES

1 Radtke T., Nevitt S.J., Hebestreit H., Kriemler S., *Physical Exercise Training for Cystic Fibrosis.* Chochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD002768. DOI: 10.1002/14651858.CD002768.pub4.

2 Radtke T., Nolan S.J., Hebestreit H., Kriemler S., *Physical Exercise training for Cystic Fibrosis.* Pediatr. Respir. Rev. 2016. DOI: 10.1016/j.prrv.2015.12.004

3 Bradley J.M., Moran F., *Physical Training for Cystic Fibrosis,* Chochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD002768. DOI: 10.1002/14651858.CD002768.pub2.

4 Shneiderman J., Wilkes D., Atenafu E.G., Nguyen T., et al., *Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis.* Eur Respir J 2014;43:817-823. DOI: 10.1183/09031936.00055513

5 Shneiderman-Walker J., Pollock S.L., Corey M., Wilkes D.D., et al., *A randomized controlled trial of 3 year home exercise program in cystic fibrosis.* The Journal of Pediatrics 2014;136, Art. No.:3. DOI: 10.1067/mpd.2000.103408

6 Moorcroft A.J., Dodd M.E., Morris J., Webb A.K., *Individualised unsupervised exercise training in adults with cystic fibrosis: a 1 year randomised controlled trial.* Thorax 2004;59:1074-1080. DOI: 10.1136/thx.2003.015313

7 Collaco J.M., Blackman S.M., Raraigh K.S., Morrow C.B., et al., *Self-reported exercise and longitudinal outcomes in cystic fibrosis: a retrospective cohort study.* BMC Pulmonary Medicine 2014;14:159. http://www.biomedcentral.com/1471-2466/14/159

8 Kriemler S., Kieser S., Junge S., Ballmann M., et al., *Effect of supervised training on FEV1 in cystic fibrosis: A randomized controlled trial.* Journal of Cystic Fibrosis 2013;12:714-720. DOI: 10.1016/j.jcf.2013.03.003

9 Tucker M., Crandall R., Seigler N., Rodriguez-Miguelez P., et al., *A single bout of maximal exercise improves lung function in patients with cystic fibrosis.* Journal of Cystic Fibrosis 2017;16: 752-758. DOI: 10.1016/j.jcf.2017.05.011

0 0 0

Other outcomes

is it worth a sentence mentioning what other outcomes there may be? I note you mention LCI later in the text.

4 0 1

Perhaps include how long the PA study went for - especially as it's a longer time frame than the studies in the next paragraph.

0 0 0

I think the flow of this section could be further improved. Maybe less short paragraphs and more of a link between these studies rather than stating studies paragraph by paragraph

0 0 0

Suggested edit:
In a study with 2 years of follow up, the control group demonstrated...

0 0 0

12h

0 0 0

Suggested edit:

Studies have evaluated the effects of different exercise interventions and dose responses on lung function.

0 0 0

I agree that there is not 'strong' evidence for the effect of exercise on lung function - consider softening the language used

0 0 0

As the summary includes physical activity, exercise training and acute exercise, it may be useful to clarify this in the summary and position statement?

0 0 0

I don't think #9 is the correct reference for this last sentence

0 0 0

I'm not sure we can conclude that there is "strong" evidence

4 0 0

I wonder whether conclusion should read that exercise and physical activity may slow rate of decline and that there may be a differential slowing between adults and children

3 0 2

clarification regarding the definition of lung health would be useful from the outset as FEV1 and LCI have been included but only FEV1 is included in the position statement

1 0 0

Can we mention how long the participants exercised for in the twin/ siblings study?

0 0 0

The flow of the summary could be improved by perhaps reducing the number of short paragraphs used

4 0 1

o_w_tomlinson + 7 · 1m

2.2 Cardiovascular Health

HEALTH BENEFITS OF PHYSICAL ACTIVITY AND EXERCISE: CARDIOVASCULAR HEALTH

Context: This statement summarises the evidence for physical activity and exercise to modify cardiovascular health in cystic fibrosis (CF). Cardiovascular health outcomes include traditional risk factors for cardiovascular disease (i.e. body composition, blood pressure and blood biomarkers), and measures of blood vessel structure and function. Physical activity and exercise literature is viewed in the broadest sense, covering both acute (i.e. single bout) and chronic (i.e. training) models. Evidence is also presented from observational and interventional study designs, and data from systematic reviews (systematic) where available.

Summary: A Cochrane review by Radtke *et al.* (1) identified 11 exercise training studies in CF that examined body size and composition outcomes. The review found no consistent evidence for improvements in body mass, body mass index or markers of body composition (fat free mass, body fat percentage) and the evidence was deemed of a low quality. This review also identified one study that measured blood biomarkers following a combined aerobic and anaerobic exercise intervention in adults with CF. Despite no changes in glycosylated haemoglobin (a marker of 3-month glycaemic control), the exercise group reported improvements in the glucose and insulin responses to an oral glucose tolerance test and improvement in insulin sensitivity. However, as this is only a single study, the quality of evidence was graded low. No other cardiovascular health outcomes were reported in the Radke et al. (2017) review. One of the studies in the review measured systolic blood pressure at baseline of a 3-year home-based aerobic exercise programme, but did not report the intervention effect (2). More recent exercise training intervention studies do include cardiovascular health outcomes, but only report these as baseline data (i.e. (3)). Finally, there are promising results showing exercise training may improve additional markers of cardiovascular health, such as heart rate variability, in CF (4) but more evidence is needed.

The CF literature has largely focussed on associations between physical activity and physical fitness, lung function and bone health, rather than cardiovascular outcomes. There is evidence to suggest that physical activity may be positively related to body mass percentile in children and adolescents with CF, especially in patients with mild to severe disease (5,6). However, these associations are cross-sectional, are not adjusted for other important confounders, and this is not a consistent relationship reported in the literature (e.g. (7)). Therefore, there is currently a low quality of evidence to support an association between physical activity and cardiovascular health outcomes in CF.

Although there is evidence of increased arterial stiffness and a reduction in large and small vessel function in CF, there are spare data on the potential for physical activity and/or exercise to reverse these vascular outcomes in CF. Vascular endothelial function is related to markers of aerobic fitness in CF (8). As aerobic fitness and physical activity have been shown to be related in CF (e.g. (9)), this suggests a putative relationship between vascular outcomes and physical activity, but this has yet to be explored. Using an acute exercise model, adults with CF have been shown to increase blood flow during forearm exercise with no differences to healthy controls, suggesting a similar exercise hyperaemic response to acute exercise (10). There are also data to suggest adults with CF may experience a transient increase in central arterial stiffness in response to a bout aerobic cycling exercise (11). However, these observations have yet to be replicated and the effect of physical activity and exercise interventions on arterial stiffness and large and small vessel function in CF are yet to be established.

Position Statement: There is currently insufficient evidence to support physical activity and exercise to improve markers of cardiovascular health in cystic fibrosis.

REFERENCES

1. Radtke T, Nevitt SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. Cochrane Database of Systematic Reviews. 2017/11/02 ed. 2017 Nov;11:CD002768.
2. Schneiderman-Walker J, Pollock SL, Corey M, Wilkes DD, Canny GJ, Pedder L, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. The Journal of Pediatrics. 2000;136(3):304–10.
3. Gupta S, Mukherjee A, Lodha R, Kabra M, Deepak KK, Khadgawat R, et al. Effects of Exercise Intervention Program on Bone Mineral Accretion in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial. Indian Journal of Pediatrics. 2019/07/10 ed. 2019;
4. Estévez-González AJ, Donadio MVF, Cobo-Vicente F, Fernández-Luna Á, Sanz-Santiago V, Villa Asensi JR, et al. Effects of a Short-Term Resistance-Training Program on Heart Rate Variability in Children With Cystic Fibrosis-A Randomized Controlled Trial. Frontiers in Physiology. 2021;12:652029.
5. Boucher GP, Lands LC, Hay JA, Hornby L. Activity levels and the relationship to lung function and nutritional status in children with cystic fibrosis. American Journal of Physical Medicine & Rehabilitation. 1997;76(4):311–5.
6. Selvadurai HC, Blimkie CJ, Cooper PJ, Mellis CM, Van Asperen PP. Gender differences in habitual activity in children with cystic fibrosis. Archives of Disease in Childhood. 2004;89(10):928–33.
7. Nixon PA, Orenstein DM, Kelsey SF. Habitual physical activity in children and adolescents with cystic fibrosis. Medicine and Science in Sports and Exercise. 2001;33(1):30–5.
8. Poore S, Berry B, Eidson D, McKie KT, Harris RA. Evidence of vascular endothelial dysfunction in young patients with cystic fibrosis. Chest. 2013;143(4):939–45.
9. Hebestreit H, Kieser S, Rüdiger S, Schenk T, Junge S, Hebestreit A, et al. Physical activity is independently related to aerobic capacity in cystic fibrosis. European Respiratory Journal. 2006;28(4):734–9.
10. Schrage WG, Wilkins BW, Dean VL, Scott JP, Henry NK, Wylam ME, et al. Exercise hyperemia and vasoconstrictor responses in humans with cystic fibrosis. Journal of Applied Physiology. 2005;99(5):1866–71.
11. Hull JH, Ansley L, Bolton CE, Sharman JE, Knight RK, Cockcroft JR, et al. The effect of exercise on large artery haemodynamics in cystic fibrosis. Journal of Cystic Fibrosis. 2011;10(2):121–7.

0 0

Should all sections have a "context" section?? Sets scene nicely here...

0 0

minor edit required - systematic reviews (systematic)

2 0

Perhaps the information regarding glycemic control would be better suited to a different section. As, while it is certainly associated with cardiovascular health, it isn't a marker of cardiac and vascular function *se*.

2 0

May be important to add what improtant confounders exist (for example....)

3 0

typo - 'focused'

1 0

Add references here and also include the literature on heart function using LV strain.

4 0

Did you mean there are 'sparse' data

1 0

Worth saying re physical activity above certain intensity??

1 0 1

Is it work adding 'future directions' as with other sections? Particularly related to aging and CVD in CF

1 0

<< Similar to this comment: Would it be worth noting the evidence / recommendations for healthy people given the ageing population of people with CF

3 0

what is the strongest evidence to state a sentence in the positive. Which variable has the strongest evidence base from a cardiovascular perspective?

0 0

o_w_tomlinson + 6 · 1m

2.3 Musculoskeletal Health

MUSCULOSKELETAL HEALTH (INCLUDING MUSCLE, BONE AND BODY COMPOSITION)

Musculoskeletal alterations exist in pwCF and have various clinical consequences. PwCF have reductions in both muscle mass and strength, with lower limbs muscles being generally more affected (1-3), and these alterations are associated with reduced whole-body exercise performance (4-7). It is of note that recent improvements in treatment and management of CF have resulted in significant improvements in nutritional status, and caution is needed when extrapolating findings obtained over the past several decades to the current CF generation. However, recent reports still indicate a high prevalence of fat-free mass (FFM) depletion in young pwCF, which is associated with worse clinical outcomes (Ritchie JCF 2021), demonstrating the importance of developing exercise interventions that target both structural and functional muscle alterations.

Most studies using aerobic training alone or combined with resistance training in pwCF did not find improvements in FFM (8-10). However, resistance training alone or combined with aerobic training was effective in improving muscle strength in several studies (8, 10, 11), highlighting that short-term changes in muscle strength are possible in the absence of muscle hypertrophy and are most likely related to neural factors. Obtaining positive changes in muscle mass may require longer training duration and/or individualized resistance training programs with appropriate volume and intensity tailored to an individual. For instance, an in-hospital supervised resistance training program resulted in improvements in both muscle mass and strength in children with CF whereas endurance training did not (12) . PwCF who cannot engage in conventional exercise strategies (e.g. during severe exacerbation, pre- and post-transplant) may also benefit from adjunct approaches such a neuromuscular stimulation (NMES). Six weeks of NMES performed prior to 8 weeks of aerobic training increased thigh circumference and quadriceps strength and decreased dyspnea on 6MWT, compared to controls (i.e. same aerobic training without prior NMES) in adults with CF and severe lung disease (13).

Increased life expectancy for pwCF also presents new issues for chronic musculoskeletal diseases that present later in adult life, such as osteopenia and osteoporosis (14). Cross sectional studies suggest a beneficial effect of exercise and PA on CF bone health, as greater PA levels and aerobic capacity are associated with higher bone mineral density (15, 16). However, data regarding the impacts of an exercise training regimen on bone health in pwCF are very limited. A lone RCT involving one year of resistance training in children and adolescents with CF did not find significant changes on bone mineral density determined by dual energy X-ray absorptiometry (17). However, the exercise programme was unsupervised, and no measurements of muscle function were performed which casts doubt on whether a sufficient training stimulus was achieved.

Position Statement: There is some evidence that pwCF have structural and functional muscle alterations contributing to reduced exercise performance, and that resistance training improves muscle strength. Additional studies are necessary to accurately quantify changes in FFM in response to exercise, with data collection modalities (e.g. magnetic resonance imaging) that can measure localized muscle volume in the specifically trained muscles. The effect of exercise interventions on bone health in pwCF are currently unclear. Future studies should test the effectiveness of supervised weight bearing exercise interventions and extend the interventions to the growing cohort of older adults with CF as the prevalence of osteoporosis and osteopenia increase with age in CF. As the combination of over-nutrition and improved CFTR function can alter energy balance and will further promote weight gain (18), future trials enrolling overweight and obese pwCF should also consider modulation in fat mass as a primary endpoint.

REFERENCES

1. Elkin SL, Williams L, Moore M, Hodson ME, Rutherford OM. Relationship of skeletal muscle mass, muscle strength and bone mineral density in adults with cystic fibrosis. Clin Sci (Lond). 2000;99(4):309-14.
2. Gruet M, Troosters T, Verges S. Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical implications and response to therapeutic interventions. J Cyst Fibros. 2017;16(5):538-52.
3. Bolton CE, Ionescu AA, Evans WD, Pettit RJ, Shale DJ. Altered tissue distribution in adults with cystic fibrosis. Thorax. 2003;58(10):885-9.
4. de Meer K, Gulmans VA, van Der Laag J. Peripheral muscle weakness and exercise capacity in children with cystic fibrosis. Am J Respir Crit Care Med. 1999;159(3):748-54.
5. Ruf K, Beer M, Kostler H, Weng AM, Neubauer H, Klein A, et al. Size-adjusted muscle power and muscle metabolism in patients with cystic fibrosis are equal to healthy controls - a case control study. BMC Pulm Med. 2019;19(1):269.
6. Gruet M, Decorte N, Mely L, Vallier JM, Camara B, Quetant S, et al. Skeletal muscle contractility and fatigability in adults with cystic fibrosis. J Cyst Fibros. 2016;15(1):e1-8.
7. Troosters T, Langer D, Vrijsen B, Segers J, Wouters K, Janssens W, et al. Skeletal muscle weakness, exercise tolerance and physical activity in adults with cystic fibrosis. Eur Respir J. 2009;33(1):99-106.
8. Santana Sosa E, Groeneveld IF, Gonzalez-Saiz L, Lopez-Mojares LM, Villa-Asensi JR, Barrio Gonzalez MI, et al. Intrahospital weight and aerobic training in children with cystic fibrosis: a randomized controlled trial. Med Sci Sports Exerc. 2012;44(1):2-11.
9. Hebestreit H, Kieser S, Junge S, Ballmann M, Hebestreit A, Schindler C, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. Eur Respir J. 2010;35(3):578-83.
10. Beaudoin N, Bouvet GF, Coriati A, Rabasa-Lhoret R, Berthiaume Y. Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis. Med Sci Sports Exerc. 2017;49(2):231-7.
11. Rovedder PM, Flores J, Ziegler B, Casarotto F, Jaques P, Barreto SS, et al. Exercise programme in patients with cystic fibrosis: a randomized controlled trial. Respir Med. 2014;108(8):1134-40.
12. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. Pediatr Pulmonol. 2002;33(3):194-200.
13. Vivodtzev I, Decorte N, Wuyam B, Gonnet N, Durieu I, Levy P, et al. Benefits of neuromuscular electrical stimulation prior to endurance training in patients with cystic fibrosis and severe pulmonary dysfunction. Chest. 2013;143(2):485-93.
14. Chedevergne F, Sermet-Gaudelus I. Prevention of osteoporosis in cystic fibrosis. Curr Opin Pulm Med. 2019;25(6):660-5.
15. Tejero Garcia S, Giraldez Sanchez MA, Cejudo P, Quintana Gallego E, Dapena J, Garcia Jimenez R, et al. Bone health, daily physical activity, and exercise tolerance in patients with cystic fibrosis. Chest. 2011;140(2):475-81.
16. Frangolias DD, Paré PD, Kendler DL, Davidson AGF, Wong L, Raboud J, et al. Role of exercise and nutrition status on bone mineral density in cystic fibrosis. Journal of Cystic Fibrosis. 2003;2(4):163-70.
17. Gupta S, Mukherjee A, Lodha R, Kabra M, Deepak KK, Khadgawat R, et al. Effects of Exercise Intervention Program on Bone Mineral Accretion in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial. Indian J Pediatr. 2019;86(11):987-94.
18. Litvin M, Yoon JC, Leey Casella J, Blackman SM, Brennan AL. Energy balance and obesity in individuals with cystic fibrosis. J Cyst Fibros. 2019;18 Suppl 2:S38-S47.

0 0 1

there are some data to demonstrate skeletal muscle mitochondrial dysfunction in PwCF (erickson, 2015)

0 0 1

might also be good to add the difference in exercise capacity that was only observed when normalizing VO2 for FFM (Fielding 2015)

2 0 3

Stretching and flexibility exercises are commonly prescribed by physios, particularly for thoracic / rib cage to maintain musculoskeletal health. Not sure if any RCT's conducted in this area?? But should we include that angle in this section?? See section 10.7 of Physiotherapy standards of care document from CF Trust

1 0 1

I do wonder whether the 'optimal training' section should be absorbed elsewhere, as there is cross over with this section and other previous sections

0 0

I think the position statement is too long and should be factual. Separate into 2 statements and perhaps remove the reference to what future studies are needed....

5 0 2

For your statement are you not stating that:

Strength training is important to not only increase muscle strength for pwCf, but also has favourable impacts on bone health and body fa and muscle mass.

0 0 2

Your quote preceding reference 12 is a little at odds with another submission on "optimal training" which highlights the importance of aerobic training

0 0

Bone Health

Helen Buntain and colleagues (Thorax 2004) demonstrated that PA correlated with bone density

Hind et al. J CF showed that exercise has effect on preservation of bone density

0 0 1

CFTR

Evidence exists for CFTR expression in muscle and bone - it is not just the weight angle that may impact these functions; may be a direct CFTR enabling effect?? I'm sure that there are references to support the CFTR channel being present in these tissues

0 0

b_w_tomlinson + 6 · 1m

2.4 Fitness

HEALTH BENEFITS OF ACTIVITY AND EXERCISE ON FITNESS

The health benefits of activity and exercise on fitness in Cystic Fibrosis (CF) have been extensively researched. Numerous randomised control trials, involving interventions that varied in type of exercise, intensity of exercise, and duration of intervention have been conducted in in-patient outpatient and home settings, with varying levels of healthcare staff supervision[1–16]. Some of these studies were well powered [6,11] whilst others had significant follow up periods [5,12]. Overall, a Cochran database systematic review concluded that there was some evidence that exercise is beneficial for aerobic fitness, and that no negative side effects of exercise exist for people with CF [17]

The effect of exercise on increasing and maintaining fitness has been quantified predominantly through the measurement of peak oxygen uptake ($V'O_2peak$) [1,3–8,11–14]. One well powered study [12], found that a six month, home based conditioning programme significantly ($p<0.01$) increased $V'O_2peak$ in a sample of people with CF, aged between 12-40. These improvements were maintained more than a year after the intervention had ended, with authors suggesting the intervention encouraged participants to continue new exercise habits and therefore, maintain fitness too. Another study found 3 months of supervised anaerobic training intervals produced a statistically significant 5% increase in $V'O_2peak$ [14]. Shorter duration interventions have also been shown to be effective, with 8 weeks of supervised out-patient exercise sessions, delivered in hospital also reporting improvements in $V'O_2peak$ (increases of $3.9mL.kg^{-1}.min^{-1}$ $p=0.002$) [4]. Interestingly, these gains in $V'O_2peak$ were lost ($-3.4mL.kg^{-1}.min^{-1}$ $p=0.001$) following a 4-week detraining period, when participants were instructed not to exercise. This illustrates the trainability of fitness in people with CF, despite ongoing disease processes. Of note, anaerobic training has been shown to produce some sustained benefits in anaerobic performance [14].

Some limitations to the outcome measures used when measuring fitness in CF have been highlighted. One 3 year home-based intervention failed to report improvements in fitness, however it was suggested that this was due to high levels of participants fitness at baseline, limiting potential for improvement in $V'O_2peak$ [5]. Two studies identified possible limitations to measurement of the effect of an exercise intervention due to the 6MWT not being sensitive enough to detect change after treatment [7,16]. It is possible that these factors have led to the effect of exercise on fitness in people with CF to be underestimated across the evidence base.

The evidence shows that home-based exercise, designed around patient preference, not directly supervised by healthcare staff are effective in improving fitness, thereby reducing requirement to physically attend the CF centre[12,15]. However, it should be noted, that fitness and strength can also be increased with intervention during hospital admission for an infective exacerbation in patients with CF [7]. Engaging individuals in long term exercise routines regardless of setting is of key importance.

Higher intensity interventions seemed to gain better results, suggesting the presence of a dose response of exercise on fitness. A plyometric and weights based programme resulted in significant increases in $V'O_2peak$ ($4.15mL.kg^{-1}.min^{-1}$ $p=0.006$) [11]. Two separate interventions [1,13] did not see an improvement in aerobic fitness. Both speculated that this was due to insufficient frequency and a lack of a guidance for training intensity. Identifying optimal frequency, intensity, duration and type of exercise to the CF population, rather than assessing if exercise is superior to non-treatment, should be the focus of further research on fitness in CF.

Position Statement: There is overwhelming evidence that activity and exercise at sufficient intensity and duration improves fitness and strength in the Cystic Fibrosis patient population.

References

[1] Beaudoin N, Bouvet GF, Coriati A, Rabasa-Lhoret R, Berthiaume Y. Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis. Med Sci Sports Exerc 2017;49:231–7. doi:10.1249/MSS.0000000000001104.

[2] Cerny FJ. Relative effects of bronchial drainage and exercise for in-hospital care of patients with cystic fibrosis. Phys Ther 1989;69:633–9. doi:10.1093/ptj/69.8.633.

[3] Santana-Sosa E, Gonzalez-Saiz L, Groeneveld IF, Villa-Asensi JR, De Aguero MIBG, Fleck SJ, et al. Benefits of combining inspiratory muscle with "whole muscle" training in children with cystic fibrosis: A randomised controlled trial. Br J Sports Med 2014;48:1513–7. doi:10.1136/bjsports-2012-091892.

[4] Sosa ES, Groeneveld IF, Gonzalez-Saiz L, López-Mojares LM, Villa-Asensi JR, Gonzalez MIB, et al. Intrahospital weight and aerobic training in children with cystic fibrosis: A randomized controlled trial. Med Sci Sports Exerc 2012;44:2–11. doi:10.1249/MSS.0b013e318228c302.

[5] Schneiderman-Walker J, Pollock SL, Corey M, Wilkes DD, Canny GJ, Pedder L, et al. A randomized controlled trial of a 3-year home exercise program in cystic fibrosis. J Pediatr 2000;136:304–10. doi:10.1067/mpd.2000.103408.

[6] Orenstein DM, Hovell MF, Mulvihill M, Keating KK, Hofstetter CR, Kelsey S, et al. Strength vs aerobic training in children with cystic fibrosis: A randomized controlled trial. Chest 2004;126:1204–14. doi:10.1378/chest.126.4.1204.

[7] Vivodtzev I, Decorte N, Wuyam B, Gonnet N, Durieu I, Levy P, et al. Benefi ts of neuromuscular electrical stimulation prior to endurance training in patients with cystic fibrosis and severe pulmonary dysfunction. Chest 2013;143:485–93. doi:10.1378/chest.12-0584.

[8] Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. Pediatr Pulmonol 2002;33:194–200. doi:10.1002/ppul.10015.

[9] De Oliveira ACN, De Oliveira JCM, Mesquita-Ferrari RA, Damasceno N, Oliveira LVF, Sampaio LMM. Inflammatory process modulation in children with cystic fibrosis submitted to aerobic training. Arch Med Sci 2009;5:422–6.

[10] Del Corral T, Cebrià Iranzo MÀ, López-de-Uralde-Villanueva I, Martínez-Alejos R, Blanco I, Vilaró J. Effectiveness of a home-based active video game programme in young cystic fibrosis patients. Respiration 2018;95:87–97. doi:10.1159/000481264.

[11] Gupta S, Mukherjee A, Lodha R, Kabra M, Deepak KK, Khadgawat R, et al. Effects of Exercise Intervention Program on Bone Mineral Accretion in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial. Indian J Pediatr 2019;86:987–94. doi:10.1007/s12098-019-03019-x.

[12] Hebestreit H, Kieser S, Junge S, Ballmann M, Hebestreit A, Schindler C, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. Eur Respir J 2010;35:578–83. doi:10.1183/09031936.00062409.

[13] Hommerding PX, Baptista RR, Makarewicz GT, Schindel CS, Donadio MVF, Pinto LA, et al. Effects of an educational intervention of physical activity for children and adolescents with cystic fibrosis: A randomized controlled trial. Respir Care 2015;60:81–7. doi:10.4187/respcare.02578.

[14] Klijn PHC, Oudshoorn A, Van Der Ent CK, Van Der Net J, Kimpen JL, Helders PJM. Effects of anaerobic training in children with cystic fibrosis: A randomized controlled study. Chest 2004;125:1299–305. doi:10.1378/chest.125.4.1299.

[15] Moorcroft AJ, Dodd ME, Morris J, Webb AK. Individualised unsupervised exercise training in adults with cystic fibrosis: A 1 year randomised controlled trial. Thorax 2004;59:1074–80. doi:10.1136/thx.2003.015313.

[16] Rovedder PME, Flores J, Ziegler B, Casarotto F, Jaques P, Barreto SSM, et al. Exercise programme in patients with cystic fibrosis: A randomized controlled trial. Respir Med 2014;108:1134–40. doi:10.1016/j.rmed.2014.04.022.

[17] Radtke T, Nolan SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. Cochrane Database Syst Rev 2015;6:CD002768. doi:10.1002/14651858.CD002768.pub3.

0 0

Terms

May be useful to define fitness in the context of the statement from the start?

Whee possible, also indicate what fitness measures are being reported in the example studies below. Fitness is a brad concept and we should try to be as specific as possible.

3 0 1

I like that you are reporting the magnitude of change here - could do this for the above studies where only the p value is given?

I wonder if in the statement we can consider if this increase is clinically meaningful?

0 0

---

what evidence are you using to interpret the dose response in this sentence?

0 0

Is this aerobic fitness?

Do you think the evidence is supportive for exercise rather than physical activity per se?

1 0 2

This section is clear and well written. Perhaps section 1.1 could be used to set up this section rather than covering similar topics

0 0

Cochrane

Misspelt in para 1

0 0

Ages should have units on for clarity

0 0

---

spelling - Cochrane

0 0

I suggest that anaerobic training is a term best avoided as the types of exercise described have significant aerobic contributions due to the length of the exercise bouts and many of the benefits being obtained during recovery. Therefore, HIIT may be a better description than anaerobic

2 0

There is repetition between some sections particularly around the mode/dose of exercise training

1 0

Craig's comment : are we able to precise the sufficent intensity and uration any more in this sentence for the statement as it is very descriptive?

Would it be better to state soemthing like Fitness is modifiable through frequent moderate and vigorous intensity in aerobic and strength exercise for people with CF.

0 0

o_w_tomlinson + 6 · 2mo

2.5 Other Health

OTHER PHYSICAL HEALTH BENEFITS (INCLUDING ENDOCRINE AND INFLAMMATORY FUNCTION)

Several endocrine disorders are associated with cystic fibrosis (CF), these include bone disease (see section: Musculoskeletal health), male hypogonadism, delayed puberty and CF-related diabetes (CFRD) [1]. CFRD is the most common endocrine complication [1,2], affecting approximately a third of adults with CF [3,4]. CFRD is a distinct subtype of diabetes mellitus having aspects of both type I and II diabetes mellitus, characterised by post-prandial hyperglycaemia due to insulin insufficiency [1,2,5]. Current treatment for CFRD is predominately insulin therapy [1,6], however emerging data is indicating CFTR modulator medications may reduce the need for insulin in individuals with CFRD [5]. In non-CF diabetes, exercise training interventions are recommended to improve blood glucose control, particularly in people with type II diabetes [7,8].

While the onset of dysglycaemia is associated with a reduced exercise capacity in both paediatric and adult populations with CF [9,10], there is scarce evidence investigating the effects of exercise training interventions on glycaemic control in CFRD, with two clinical trials currently underway (NCT03653949 [11]; NCT02456103 [12]). A single study has shown improved glycaemic control in 14 individuals with CFRD and dysglycaemia following a 12-week combined aerobic and resistance training programme [13]. The potential risk of hypoglycaemia with exercise has been reported as having a low incidence in CFRD [14] and moderate aerobic exercise with precautions such as checking blood glucose before exercise, extra carbohydrate snacks or altered insulin doses with vigorous exercise is recommended by the current guidelines [2,15].

The occurrence of hyperglycaemic events – in addition to respiratory, cardiovascular, metabolic and skeletomuscular diseases – result in chronic low-grade inflammation and systemic oxidative stress in people with CF [16,17]. While pharmacological interventions (e.g. CFTR modulators) relieve inflammation and oxidative stress by upregulating anti-inflammatory and -oxidant transcriptional factors at the cellular level [18], conflicting evidence in humans results in a requirement for adjuvant therapies [19]. One such intervention is exercise training, and the resultant improvements in physical fitness, which are associated with a reduction in inflammation and oxidative stress in healthy humans [20]; however, the evidence in people with CF is unclear.

Exercise training in people with CF was not reported to modulate c-reactive protein [13,21,22]. Furthermore, c-reactive protein was either indifferent [23] or lower [24] in those who are considered physically active, compared to their sedentary counterparts. Exercise training was also not reported to modulate cytokine expression in the blood of humans with CF [13,21]. Preliminary evidence suggests that exercise training upregulates YKL-40, which could be a signalling factor for enhanced muscle insulin sensitivity [13]. In contrast, a marker of bacterial infection-associated inflammation, procalcitonin, was downregulated by exercise training [21]. Neither antioxidants or biomarkers of oxidative stress were differentially modulated during exercise between people with CF and their healthy counterparts [25]; however, no studies have investigated the effect of longer-term exercise training on redox biomarkers in people with CF. As such, it is unclear whether exercise training is an effective intervention to reduce inflammation and oxidative stress in people with CF.

Position Statements

1. Evidence for the benefits of exercise in the management of glycaemic control is scarce, but indications of improved glycaemic control with low incidence of hypoglycaemic events led to recommendations for moderate activity or exercise for people with CF-related dysglycaemia.

2. Exercise interventions may modulate inflammation associated with muscle insulin sensitivity and bacterial infection. However, future research determining whether exercise training can affect oxidative stress is warranted.

Reference List

[1] Blackman SM, Tangpricha V. Endocrine Disorders in Cystic Fibrosis. Pediatr Clin North Am 2016;63:699–708. https://doi.org/10.1016/j.pcl.2016.04.009.

[2] Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, et al. Clinical Care Guidelines for Cystic Fibrosis–Related Diabetes A position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care 2010;33:2697–708. https://doi.org/10.2337/dc10-1768.

[3] Cystic Fibrosis Foundation. Patient Registry: Annual Data Report. 2019.

[4] UK Cystic Fibrosis Registry. Annual Data Report. 2019.

[5] Gaines H, Jones KR, Lim J, Medhi NF, Chen S, Scofield RH. Effect of CFTR modulator therapy on cystic fibrosis-related diabetes. J Diabetes Complications 2021;35:107845. https://doi.org/10.1016/j.jdiacomp.2020.107845.

[6] Siwamogsatham O, Alvarez JA, Tangpricha V. Diagnosis and treatment of endocrine comorbidities in patients with cystic fibrosis. Curr Opin Endocrinol Diabetes Obes 2014;21:422–9. https://doi.org/10.1097/MED.0000000000000096.

[7] Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, et al. Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association. Diabetes Care 2016;39:2065–79. https://doi.org/10.2337/dc16-1728.

[8] Thomas D, Elliott EJ, Naughton GA. Exercise for type 2 diabetes mellitus. Cochrane Database Syst Rev 2006:CD002968. https://doi.org/10.1002/14651858.CD002968.pub2.

[9] Causer AJ, Shute JK, Cummings MH, Shepherd AI, Wallbanks SR, Allenby MI, et al. The implications of dysglycaemia on aerobic exercise and ventilatory function in cystic fibrosis. J Cyst Fibros 2019. https://doi.org/10.1016/j.jcf.2019.09.014.

[10] Foster K, Huang G, Zhang N, Crisalli J, Chini B, Amin R, et al. Relationship between exercise capacity and glucose tolerance in cystic fibrosis. Pediatr Pulmonol 2017. https://doi.org/10.1002/ppul.23906.

[11] Monteiro KS, Azevedo M de P, Jales LM, da Silva FEP, Arrais RF, de Mendonça KMPP. Effects of aerobic interval training on glucose tolerance in children and adolescents with cystic fibrosis: a randomized trial protocol. Trials 2019;20:768. https://doi.org/10.1186/s13063-019-3803-8.

[12] Hebestreit H, Lands LC, Alarie N, Schaeff J, Karila C, Orenstein DM, et al. Effects of a partially supervised conditioning programme in cystic fibrosis: an international multi-centre randomised controlled trial (ACTIVATE-CF): study protocol. BMC Pulm Med 2018;18:31. https://doi.org/10.1186/s12890-018-0596-6.

[13] Beaudoin N, Bouvet GF, Coriati A, Rabasa-Lhoret R, Berthiaume Y. Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis. Med Sci Sport Exerc 2017;49:231–7. https://doi.org/10.1249/MSS.0000000000001104.

[14] Ruf K, Winkler B, Hebestreit A, Gruber W, Hebestreit H. Risks associated with exercise testing and sports participation in cystic fibrosis. J Cyst Fibros 2010;9:339–45. https://doi.org/10.1016/j.jcf.2010.05.006.

[15] Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF). Standards of Care and Good Clinical Practice for the Physiotherapy Management of cystic fibrosis.

[16] Causer AJ, Shute JK, Cummings MH, Shepherd AI, Gruet M, Costello JT, et al. Circulating biomarkers of antioxidant status and oxidative stress in people with cystic fibrosis: A systematic review and meta-analysis. Redox Biol 2020;32. https://doi.org/10.1016/j.redox.2020.101436.

[17] Nichols DP, Chmiel JF. Inflammation and its genesis in cystic fibrosis. Pediatr Pulmonol 2015;50:S39–56. https://doi.org/10.1002/ppul.23242.

[18] Borcherding DC, Siefert ME, Lin S, Brewington J, Sadek H, Clancy JP, et al. Clinically approved CFTR modulators rescue Nrf2 dysfunction in cystic fibrosis airway epithelia. J Clin Invest 2019;129:3448–63. https://doi.org/10.1172/JCI96273.

[19] Kopp BT, Zhang S, Shrestha C. Influence of CFTR Modulators on Immune Responses in Cystic Fibrosis. B94. BEST Pediatr., American Thoracic Society; 2019, p. A4008–A4008. https://doi.org/10.1164/ajrccm-conference.2019.199.1_MeetingAbstracts.A4008.

[20] Allen J, Sun Y, Woods JA. Exercise and the Regulation of Inflammatory Responses. vol. 135. 1st ed. Elsevier Inc.; 2015. https://doi.org/10.1016/bs.pmbts.2015.07.003.

[21] Vivodtzev I, Decorte N, Wuyam B, Gonnet N, Durieu I, Levy P, et al. Benefits of Neuromuscular Electrical Stimulation Prior to Endurance Training in Patients With Cystic Fibrosis and Severe Pulmonary Dysfunction. Chest 2013;143:485–93. https://doi.org/10.1378/chest.12-0584.

[22] De Oliveira ACN, De Oliveira JCM, Mesquita-Ferrari RA, Damasceno N, Oliveira LVF, Sampaio LMM. Inflammatory process modulation in children with cystic fibrosis submitted to aerobic training. Arch Med Sci 2009;5:422–6.

[23] Nigro E, Polito R, Elce A, Signoriello G, Iacotucci P, Carnovale V, et al. Physical Activity Regulates TNFα and IL-6 Expression to Counteract Inflammation in Cystic Fibrosis Patients. Int J Environ Res Public Health 2021;18:4691. https://doi.org/10.3390/ijerph18094691.

[24] Polito R, Nigro E, Elce A, Monaco ML, Iacotucci P, Carnovale V, et al. Adiponectin Expression Is Modulated by Long-Term Physical Activity in Adult Patients Affected by Cystic Fibrosis. Mediators Inflamm 2019;2019. https://doi.org/10.1155/2019/2153934.

[25] Tucker MA, Berry B, Seigler N, Davison GW, Quindry JC, Eidson D, et al. Blood flow regulation and oxidative stress during submaximal cycling exercise in patients with cystic fi brosis. J Cyst Fibros 2017. https://doi.org/10.1016/j.jcf.2017.08.015.

0 0 0

probably don't need last sentence of first paragraph

0 0 0

Is first paragraph a bit too long? Do you need that level of detail on CFRD that is not related to exercise?

0 2 0

This extends to type I too.

0 0 0

Hyperglycemia?

Any data on the risk of hyperglycaemia with vigorous intensity exercise?

1 0 2

There are also some references to hypo/hyperglycaemic events in the 'Risks of Activity & Exercise' section - may be of use?

0 0 0

Could specify the type of training that was undertaken - i.e. was it moderate intensity continuous exercise, interval training etc. Would be nice to consider if a particular training mode elicits more inflammation

1 0 0

Thanks for compiling this information in such a comprehensive fashion. I agree with the suggestion regarding including details on the type of exercise training undertaken in the studies/of value in improving glycemic control/inflammation. It might also be helpful to indicate if the studies are in children or adults (or both) - and/or whether the relationships may apply irrespective of age? It may be preferred to keep the content specific to exercise alone, as you have done. However, there is this paper which describes the relationship between PA and inflammation in adults with CF that may be useful to include: Burton et al Physiother Theory Pract 2020 Dec;36(12):1457-1465. doi: 10.1080/09593985.2019.1566942. Epub 2019 Jan 27.

1 0 0

not sure we need the future research sentence at the end of the statement as it detracts form the overall message.

0 0 0

Could we rephrase statement #1 to read something like "Improved glycaemic control with low incidence of hypoglycaemic events can be promoted, for people with CF-related dysglycaemia, by participating in moderate activity or exercise."

0 0 0

o_w_tomlinson + 8 · 1m

2.6 Mental Health

PHYSICAL ACTIVITY FOR MENTAL HEALTH

Aim

The aim of this review is to investigate the impact of physical activity and exercise on psychological problems (depression, anxiety, quality of life, emotional wellbeing, stress) in people with CF.

Methods

We systematically searched the literature for studies that explored the impact of physical activity on mental health.

Results

We identified 14 studies that met our inclusion criteria. Studies were clinically, methodologically and statistically heterogeneous. Interventions were variable in terms of content, frequency, duration, and setting. Intervention fidelity was rarely reported. Studies were also variable in terms of design, target population, and choice of outcome.

Prescribed exercise programs

The evidence for the effectiveness of prescribed exercise programs is mixed. One small randomised controlled trial [1] of hospital based anaerobic exercise found no significant effect of intervention on emotional quality of life. One small prospective study of low impact aerobic exercise [2] found no impact of intervention on wellbeing. However, a small (N=12) prospective study of aerobic and strength training combined with stretching and postural advice [3], a small (N=40) randomised trial of aerobic and strength training [4] and a small (N=14) controlled trial of resistance training [5] found a significant impact of intervention on emotional quality of life.

Dance / movement based interventions

One small (N=40) randomised trial found no impact of active video games on emotional quality of life [6].

Individual exercise programs

Two small prospective studies provide some evidence for the effectiveness of a home-based individually tailored exercise programs on emotional quality of life [7, 8]. Paranjape found positive impact of individually tailored moderate to vigorous exercise on emotional quality of life [7]. Schmidt reported small improvements in emotional quality of life following participation in exercise as selected by participants [8].

Dance

One small quasi-experimental study provides some evidence for the effectiveness of dance / movement therapy during hospital stay [9]. The 24 participants in the intervention arm showed a small but significant improvement in mood as measured by the profile of mood states question in comparison to the 10 participants in the control arm.

Mindfulness based activity

Three small studies have explored the impact of mindfulness based activity. Lorenc found that 30 minutes of tai chi at home did not result in significant improvements in emotional quality of life [10]. A small prospective study of 11 participants conducted by McNamara et al found no impact of 40 minuets of yoga on anxiety and depression as measured by the hospital anxiety and depression scale and the center for Epidemiological Studies- Depression Scale for Children. There was however, a small impact of the intervention emotional wellbeing and anxiety as measured by the Speilberger State-Trait Anxiety Inventory for Children [11]. A small prospective study of 11 participants found significant improvement in emotional quality of life following participating in 50 minuets of yoga [12].

Self reported PA

Two cross sectional studies explored the impact of self-reported exercise on mental health [13, 14]. These studies suggest that self reported participation in physical exercise is associated with improved psychological well-being [13] and fatigue [14].

Position Statement: There is currently very little evidence to support the impact of physical activity on mental health. However, studies reviewed are generally small, heterogenous and of low quality. Further research is needed before any meaningful conclusions can be made.

REFERENCES

1. Klijn, P.H., et al., *Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study.* Chest, 2004. **125**(4): p. 1299-1305.
2. Dunlevy, C.L., et al., *Physiological and psychological effects of low-impact aerobic exercise on young adults with cystic fibrosis.* Journal of Cardiopulmonary Rehabilitation, 1994. **14**(1): p. 47-51.
3. Urquhart, D., et al., *Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis.* Pediatric Pulmonology, 2012. **47**(12): p. 1235-1241.
4. Rovedder, P.M.E., et al., *Exercise programme in patients with cystic fibrosis: A randomized controlled trial.* Respiratory Medicine, 2014. **108**(8): p. 1134-1140.
5. Shaw, I., et al., *Individualized supervised resistance training during nebulization in adults with cystic fibrosis.* Pakistan Journal of Medical Sciences, 2016. **32**(5): p. 1152-1157.
6. Del Corral, T., et al., *Effectiveness of a home-based active video game programme in young cystic fibrosis patients.* Respiration, 2018. **95**(2): p. 87-97.
7. Paranjape, S.M., et al., *Exercise improves lung function and habitual activity in children with cystic fibrosis.* Journal of Cystic Fibrosis.
8. Schmidt, A.M., et al., *Exercise and quality of life in patients with cystic fibrosis: A 12-week intervention study.* Physiotherapy theory and practice, 2011. **27**(8): p. 548-556.
9. Goodill, S.W., *Dance/movement therapy for adults with cystic fibrosis: Pilot data on mood and adherence.* Alternative Therapies in Health and Medicine, 2005. **11**(1): p. 76-77.
10. Lorenc, A., et al., *CF-CATS: An uncontrolled feasibility study of using tai chi for adults with cystic fibrosis.* European Journal of Integrative Medicine, 2013. **5**(6): p. 476-486.
11. McNamara, C., et al., *Yoga therapy in children with cystic fibrosis decreases immediate anxiety and joint pain.* Evidence-based Complementary and Alternative Medicine, 2016. **2016 (no pagination)**(9429504).
12. Ruddy, J., et al., *Yoga as a therapy for adolescents and young adults with cystic fibrosis: A pilot study.* Global Advances In Health and Medicine, 2015. **4**(6): p. 32-36.
13. Backstrom-Eriksson, L., et al., *Associations between genetics, medical status, physical exercise and psychological well-being in adults with cystic fibrosis.* BMJ open respiratory research, 2016. **3**(1): p. e000141.
14. Orava, C., et al., *Fatigue and levels of physical activity in adults with cystic fibrosis: A pilot study.* Pediatric Pulmonology, 2013. **36)**: p. 362.

0 0

In first sentence - "problems" might not be the best word??

6 0 1

Perhaps an introduction would be useful here to outline the prevalence of mental health conditions in individuals with CF and any CF specific risk factors. Perhaps also worth noting that PA and exercise are associated with perceived benefits for mental health in the general population and whether or not this could translate to CF populations.

3 0

Agree with others that these headings can probably be omitted; consider starting this section from 'prescribed exercise programs' onwards

1 0

Thank you for this clear and well-presented summary. It might be relevant to clarify if/which studies involved individual activity, and which ones allowed to stay active with a sibling/parent/friend

0 0

Thank you. This is very well presented and clear. Did you consider commenting on non-CF studies. Could this be extrapolated.

1 0

Position Statement

Can this be made clear it's CF specific?

1 0

Format

The format with these sub headings although good for clarity reads quite differently to the other summaries - perhaps a discussion point to ensure standardisation across summaries?

2 0 1

Whilst this format allows for clarity of each of the studies, it does not allow for as much synthesis of evidence base and comparative discussion as other sections

2 0

title as Consensus Statement rather than Position statement

0 0

I suspect there will be a general methods section for the whole document so this one can possibly be removed

1 0

Position statement

I would suggest adding 'In CF' at the end of the first sentence. Additionally, I would suggest it is worth noting no detrimental impact of these interventions (if that is the case) as I wouldn't want to discourage people from such activities and it is possible that they are beneficial despite the lack of evidence.

2 0 1

o_w_tomlinson + 7 · 1m

2.7 Quality of Life

QUALTY OF LIFE AND ACTIVITY AND EXERCISE IN CYSTIC FIBROSIS

Health related quality of life (HRQoL) is a holistic concept of a person's perception of their life and is now recognised as a very important outcome measure in Cystic Fibrosis (CF) research. It has been defined as 'a multi-dimensional construct comprised of several domains as reported by the individual eg physical, social and psychological functioning, respiratory symptoms, treatment burden and body image' (1). Despite the fact that measurement of HRQoL is now increasingly being used to evaluate the effectiveness and perceived value of interventions (2), there is limited conclusive evidence as to the effects of activity and exercise on HRQoL in individuals with CF.

To date research investigating the impact of exercise and activity on HRQoL in individuals with CF has predominantly focussed on children (3-14) and adults (15-18) with mild to moderate disease severity. Only one study (14) included individuals with severe CF lung disease. Sample sizes in all studies are relatively small with a range of 14 (15) to 76 (11) participants. In addition a variety of outcome measures have been used with the Cystic Fibrosis questionnaire (CFQ) and the revised CFQ (CFQ-R) as the most frequently used measures with the paediatric QOL inventory (13), the SF-36 scale (17) and the quality of well-being scale also implemented (7). As a result comparison between studies is difficult. Two studies included HRQoL as a primary outcome (11, 18) with HRQoL measures in all other studies included as a secondary outcome. Few studies are therefore powered to detect significant changes in HRQoL as a result of an exercise or activity intervention. The interventions are also not focussed on interventions that may have an impact on HRQoL domains specifically. One study included exercise counselling, however this study did not report any significant change in HRQoL at the end of the study (13). Interventions were a mix of home and hospital based unsupervised and supervised exercise and activity programmes which all included tailored aerobic and strength components. The duration of interventions also varied in length from 8 weeks to one year with the most common time period being 12 weeks..

Most studies show no improvement in HRQoL measures during the study intervention period (3, 5, 11, 15-17). Some studies have shown a non-significant impact on HRQoL but have reported a trend towards a positive change in some domains such as respiratory symptoms (9), subjective health perception (10) and physical functioning (12). Four studies (6-8, 18) have shown a statistically significant positive effect on a variety of HRQoL domains including well-being (7), treatment burden and emotional functioning (18), physical, emotional, social, body, treatment and respiratory symptoms (8) and overall HRQoL score (6). However these four studies all differ in duration and intervention type so specific reasons for improvements in HRQoL are difficult to ascertain.

In summary there is some weak evidence of impact of exercise and activity on some HRQoL domains in individuals with mild to moderate CF in the short term, however there is significant heterogeneity in the methodologies and results.

Position statements:

1. Health related quality of life (HRQoL) is an important and holistic outcome measure that should be included in exercise and activity intervention research but the clinical efficacy of exercise and activity interventions on the different domains of health related quality of life (HRQoL) remains unclear.

2. Future research should focus on interventions that:
- Investigate the impact when psychosocial interventions are included in parallel.
- Evaluate the dosage and intensity of exercise and activity needed to impact on HRQoL
- Use consistent and sensitive outcome measures
- Recruit individuals with a variety of disease severity

REFERENCES

1. Abbott J. Health-related quality of life measurement in cystic fibrosis: advances and limitations. Chron Respir Dis. 2009;6(1):31-41.
2. Royce FH, Carl JC. Health-related quality of life in cystic fibrosis. Curr Opin Pediatr. 2011;23(5):535-40.
3. Santana Sosa E, Groeneveld IF, Gonzalez-Saiz L, López-Mojares LM, Villa-Asensi JR, Barrio Gonzalez MI, et al. Intrahospital weight and aerobic training in children with cystic fibrosis: a randomized controlled trial. Med Sci Sports Exerc. 2012;44(1):2-11.
4. Santana-Sosa E, Gonzalez-Saiz L, Groeneveld IF, Villa-Asensi JR, Barrio Gómez de Aguero MI, Fleck SJ, et al. Benefits of combining inspiratory muscle with 'whole muscle' training in children with cystic fibrosis: a randomised controlled trial. Br J Sports Med. 2014;48(20):1513-7.
5. Hommerding PX, Baptista RR, Makarewicz GT, Schindel CS, Donadio MV, Pinto LA, et al. Effects of an educational intervention of physical activity for children and adolescents with cystic fibrosis: a randomized controlled trial. Respir Care. 2015;60(1):81-7.
6. Gupta S, Mukherjee A, Lodha R, Kabra M, Deepak KK, Khadgawat R, et al. Effects of Exercise Intervention Program on Bone Mineral Accretion in Children and Adolescents with Cystic Fibrosis: A Randomized Controlled Trial. Indian J Pediatr. 2019;86(11):987-94.
7. Selvadurai HC, Blimkie CJ, Meyers N, Mellis CM, Cooper PJ, Van Asperen PP. Randomized controlled study of in-hospital exercise training programs in children with cystic fibrosis. Pediatr Pulmonol. 2002;33(3):194-200.
8. Urquhart D, Sell Z, Dhouieb E, Bell G, Oliver S, Black R, et al. Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis. Pediatr Pulmonol. 2012;47(12):1235-41.
9. Del Corral T, Cebria IIMA, Lopez-de-Uralde-Villanueva I, Martinez-Alejos R, Blanco I, Vilaro J. Effectiveness of a Home-Based Active Video Game Programme in Young Cystic Fibrosis Patients. Respiration. 2018;95(2):87-97.
10. Hebestreit H, Kieser S, Junge S, Ballmann M, Hebestreit A, Schindler C, et al. Long-term effects of a partially supervised conditioning programme in cystic fibrosis. Eur Respir J. 2010;35(3):578-83.
11. Hebestreit H, Schmid K, Kieser S, Junge S, Ballmann M, Roth K, et al. Quality of life is associated with physical activity and fitness in cystic fibrosis. BMC Pulm Med. 2014;14:26.
12. Klijn PH, Oudshoorn A, van der Ent CK, van der Net J, Kimpen JL, Helders PJ. Effects of anaerobic training in children with cystic fibrosis: a randomized controlled study. Chest. 2004;125(4):1299-305.
13. Moola FJ, Garcia E, Huynh E, Henry L, Penfound S, Consunji-Araneta R, et al. Physical Activity Counseling for Children With Cystic Fibrosis. Respir Care. 2017;62(11):1466-73.
14. Ledger SJ, Owen E, Prasad SA, Goldman A, Willams J, Aurora P. A pilot outreach physiotherapy and dietetic quality improvement initiative reduces IV antibiotic requirements in children with moderate-severe cystic fibrosis. J Cyst Fibros. 2013;12(6):766-72.
15. Beaudoin N, Bouvet GF, Coriati A, Rabasa-Lhoret R, Berthiaume Y. Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis. Med Sci Sports Exerc. 2017;49(2):231-7.
16. Ward N, Stiller K, Rowe H, Morrow S, Morton J, Greville H, et al. Airway clearance by exercising in mild cystic fibrosis (ACE-CF): A feasibility study. Respir Med. 2018;142:23-8.
17. Rovedder PM, Flores J, Ziegler B, Casarotto F, Jaques P, Barreto SS, et al. Exercise programme in patients with cystic fibrosis: a randomized controlled trial. Respir Med. 2014;108(8):1134-40.
18. Schmidt AM, Jacobsen U, Bregnballe V, Olesen HV, Ingemann-Hansen T, Thastum M, et al. Exercise and quality of life in patients with cystic fibrosis: A 12-week intervention study. Physiother Theory Pract. 2011;27(8):548-56.

0 0

Title

The spelling of quality needs correcting in the title

4 0 1

Opening para

I really like this opening paragraph, as it defines the outcome and provides a wider context. It would be nice if all sections had this structure to start with.

What about data on fitness and HRQoL?

1 0

Suggestion

I know this one is an abstract, but it's discussed in DOI: 10.1097/MCP.0B013E32834B6AF4. Anyway, it talks about perceptions of QoL in CF adults in those who exercise Vs those who do less. Dwyer TJ, Griffin B, McKeough ZJ, *et al.* Differences in quality of life, lung function and hospitalisation rates for adults with cystic fibrosis, according to exercise participation [abstract]. J Cyst Fibros 2010; 9(S1):S69

....just thought it might fill a gap/be worth a comment about adults?

0 0

Review evidence?

I really enjoyed the narrative about the studies -this is very comprehensive. Has a review synthesised the collective evidence (i.e. Radke et al?)

1 0

Would it be relevant to add age range?

0 0

Clear, well-presented and comprehensive. Good job

0 0

3d

0 0 1

Nice section, good job

2 0

the future directions part can be positioned elsewhere - not needed in the statement at this moment in time.

0 0

Units

When reporting ages the unit (likely years) needs to be added.

0 0 1

Position Statement

Should just be one sentence

0 0 1

g_w_tomlinson + 13 1m

3.1 Measurement of Physical Activity

MEASUREMENT OF PHYSICAL ACTIVITY

Physical activity (PA), previously defined as "any bodily movement produced by skeletal muscles that results in energy expenditure" (1), is particularly broad and complex to measure (2), not least given the recent holistic definition, encompassing movement *and* the context (3). Subjective methods, such as questionnaires, diaries and log-books, are low-cost and feasible to implement, and therefore well-suited for large epidemiological studies. Such measures can provide an indication of the quantity *and* context of PA, evaluating multiple domains (i.e. leisure and daily-life activities). However, self-report methods are susceptible to recall bias (4), have low validity (5), offer low accuracy to measure different intensities (6, 7) and are usually limited by factors such as age, the complexity of questions, and health status.

Contrary to subjective methods, device-based methods, such as pedometers and accelerometers, are capable of measuring movement or the energy expended (2, 8, 9). Pedometers, which measure vertical acceleration through a spring-suspended lever, are easy to use and low-cost, but are designed to measure activities such as walking and running and can only provide an indication of volume (i.e. number of steps), rather than PA intensities and patterns (10). Alternatively, accelerometers, the most popular tool to measure PA in healthy and clinical populations, irrespective of age, have been shown to assess PA intensities in a reliable and accurate manner (2, 8, 11-13). However, the processing decisions surrounding accelerometry remain subjective, from selecting the sampling frequency (14), wear-time criteria (15) and type of data (i.e. raw vs. pre-processed; 16), to the translation of acceleration into PA patterns and intensities, such as light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA; 15, 16). Whilst traditional methods such as cut-points and prediction equations have been used to assess PA levels and energy expenditure in the cystic fibrosis (CF) population (17-19), highly accurate machine learning approaches are now being utilised in both healthy and clinical populations (20-25).

It is pertinent to note that prediction equations, cut-points, and machine learning models are population-specific and can lead to over- or under-estimation of PA intensities and energy expenditure when applied to a different population from which they were derived (26, 27). This is particularly important given the higher energetic demands characteristic of those with CF (28-30), whom require more energy to undertake activities, and even during rest, in comparison to their healthy counterparts (31, 32). It is therefore imperative that accelerometry data processing techniques are developed from CF populations. Indeed, the CF-specific prediction equations (27), cut-points (33) and machine learning models (34)developed for children were considerably different to ones developed for the general population. Mackintosh et al. (19) postulated that such discrepancies, may, at least in part, explainfindings which reported that those with CF spent less time in MVPA and more in LPA than their peers (18, 35, 36). Therefore, the development of CF-specific measurements of PA is fundamental to enhance our understanding of the relationship between PA and health, and subsequently inform interventions and recommendations in this population.

Position Statement: Accelerometers can provide more accurate information regarding the volume and accumulation of physical activity when CF-specific data processes are utilised, but self-report data is still required to provide contextual information.

REFERENCES

1. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.
2. Matthews CE, Hagströmer M, Pober DM, Bowles HR. Best Practices for Using Physical Activity Monitors in Population-Based Research. Medicine and science in sports and exercise. 2012;44(1 Suppl 1).
3. Piggin J. What Is Physical Activity? A Holistic Definition for Teachers, Researchers and Policy Makers. Frontiers in Sports and Active Living. 2020;2(72).
4. Trost SG, O'Neil M. Clinical use of objective measures of physical activity. Br J Sports Med. 2014;48(3):178-81.
5. Rangul V, Holmen TL, Kurtze N, Cuypers K, Midthjell K. Reliability and validity of two frequently used self-administered physical activity questionnaires in adolescents. BMC medical research methodology. 2008;8:47.
6. Pierce MJ-K, James FS, Elizabeth AG, Cheryl LR, John P. Comparative validation of the IPAQ and the 7-Day PAR among women diagnosed with breast cancer. International Journal of Behavioral Nutrition and Physical Activity. 2006;3(1):7.
7. Richardson MT, Ainsworth BE, Jacobs DR, Leon AS. Validation of the Stanford 7-day recall to assess habitual physical activity. Annals of epidemiology. 2001;11(2):145-53.
8. Sylvia LG, Bernstein EE, Hubbard JL, Keating L, Anderson EJ. Practical guide to measuring physical activity. J Acad Nutr Diet. 2014;114(2):199-208.
9. Ainsworth BE. How do I measure physical activity in my patients? Questionnaires and objective methods. Br J Sports Med. 2009;43(1):6-9.
10. Bassett DR, Toth LP, LaMunion SR, Crouter SE. Step Counting: A Review of Measurement Considerations and Health-Related Applications. Sports Med. 472017. p. 1303-15.
11. Arvidsson D, Fridolfsson J, Börjesson. Measurement of Physical Activity in Clinical Practice Using Accelerometers. Journal of internal medicine. 2019;286(2).
12. Lipert A, Jegier A. Comparison of Different Physical Activity Measurement Methods in Adults Aged 45 to 64 Years Under Free-Living Conditions. Clin J Sport Med. 2017;27(4):400-8.
13. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol. 332018. p. 811-29.
14. Troiano RP, McClain JJ, Brychta RJ, Chen KY. Evolution of accelerometer methods for physical activity research. Br J Sports Med. 2014;48(13):1019-23.
15. Welk GJ. Principles of design and analyses for the calibration of accelerometry-based activity monitors. Med Sci Sports Exerc. 2005;37(11 Suppl):S501-11.
16. Farrahi V, Niemelä M, Kangas M, Korpelainen R, Jämsä T. Calibration and Validation of Accelerometer-Based Activity Monitors: A Systematic Review of Machine-Learning Approaches. Gait & posture. 2019;68.
17. Cox NS, Alison JA, Button BM, Wilson JW, Morton JM, Holland AE. Physical activity participation by adults with cystic fibrosis: An observational study. Respirology. 2016;21(3):511-8.
18. Aznar S, Gallardo C, Fiuza-Luces C, Santana-Sosa E, López-Mojares LM, Santalla A, et al. Levels of moderate--vigorous physical activity are low in Spanish children with cystic fibrosis: a comparison with healthy controls. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2014;13(3):335-40.
19. Mackintosh KA, Ridgers ND, Evans RE, McNarry MA. Physical Activity and Sedentary Time Patterns in Children and Adolescents With Cystic Fibrosis and Age- and Sex-Matched Healthy Controls. J Phys Act Health. 2018;15(2):82-8.
20. Ahmadi MN, Chowdhury A, Pavey T, Trost SG. Laboratory-based and free-living algorithms for energy expenditure estimation in preschool children: A free-living evaluation. PLoS One. 2020.
21. Staudenmayer J, He S, Hickey A, Sasaki J, Freedson P. Methods to estimate aspects of physical activity and sedentary behavior from high-frequency wrist accelerometer measurements. J Appl Physiol (1985). 2015;119(4):396-403.
22. Bonomi AG, Plasqui G, Goris AHC, Westerterp KR. Improving assessment of daily energy expenditure by identifying types of physical activity with a single accelerometer. Journal of Applied Physiology. 2009;107(3):655-61.
23. Staudenmayer J, Pober D, Crouter S, Bassett D, Freedson P. An artificial neural network to estimate physical activity energy expenditure and identify physical activity type from an accelerometer. J Appl Physiol (1985). 2009;107(4):1300-7.
24. Doherty MW, Sven H, Louis A, Chris H, Aiden. Statistical machine learning of sleep and physical activity phenotypes from sensor data in 96,220 UK Biobank participants. Scientific Reports. 2018;8(1):7961.
25. Fergus P, Hussain A, Hearty J, Fairclough S, Boddy L, Mackintosh KA, et al., editors. A Machine Learning Approach to Measure and Monitor Physical Activity in Children to Help Fight Overweight and Obesity2015; Cham: Springer International Publishing.
26. Serra MC, Balraj E, DiSanzo BL, Ivey FM, Hafer-Macko CE, Treuth MS, et al. Validating accelerometry as a measure of physical activity and energy expenditure in chronic stroke. Topics in Stroke Rehabilitation. 2017;24(1):18-23.
27. Stephens S, Takken T, Esliger DW, Pullenayegum E, Beyene J, Tremblay M, et al. Validation of Accelerometer Prediction Equations in Children With Chronic Disease. Pediatric exercise science. 2016;28(1).
28. Ramsey BW, Farrell PM, Pencharz P. Nutritional assessment and management in cystic fibrosis: a consensus report. The Consensus Committee. Am J Clin Nutr. 1992;55(1):108-16.
29. Bandini LG, Schoeller DA, Fukagawa NK, Wykes LJ, Dietz WH. Body composition and energy expenditure in adolescents with cerebral palsy or myelodysplasia. Pediatr Res. 1991;29(1):70-7.
30. Epstein LH, Wing RR, Cluss P, Fernstrom MH, Penner B, Perkins KA, et al. Resting metabolic rate in lean and obese children: relationship to child and parent weight and percent-overweight change. The American Journal of Clinical Nutrition. 1989;49(2):331-6.
31. Matel JL, Milla CE. Nutrition in cystic fibrosis. Semin Respir Crit Care Med. 2009;30(5):579-86.
32. Wilkes DL, Schneiderman JE, Nguyen T, Heale L, Moola F, Ratjen F, et al. Exercise and physical activity in children with cystic fibrosis. Paediatric respiratory reviews. 2009;10(3).
33. Bianchim MS, McNarry MA, Evans R, Thia L, Barker AR, Williams CA, et al. Calibration and Cross-validation of Accelerometry in Children and Adolescents with Cystic Fibrosis. Unpublished Manuscript. 2021.
34. Bianchim MS, McNarry MA, Barker AR, Williams CA, Denford S, Thia L, et al. A Machine Learning Approach for Physical Activity Recognition in Cystic Fibrosis. Manuscript under review. 2021.
35. Selvadurai HC, Blimkie CJ, Cooper PJ, Mellis CM, Van Asperen PP. Gender differences in habitual activity in children with cystic fibrosis. Archives of disease in childhood. 2004;89(10):928-33.
36. Nixon PA, Orenstein DM, Kelsey SF. Habitual physical activity in children and adolescents with cystic fibrosis. Med Sci Sports Exerc. 2001;33(1):30-5.

1 0

Overall, i think this is very good. I just wonder if there is more literature to support the use of accelerometry as a measure of PA in CF. It seems as though there is a lot on the method itself within this 500 words, but not really summarizing the data in CF???

4 0 2

Bias

Clarify the direction, and issue? Over reporting, inflate associations with health outcomes?

0 0

I wonder should this include the measurement of sedentary behaviour too?? Different to lack of habitual physical activity but equally important if mentioning accelerometers

4 0

Are higher energetic demands still relevant in the relatively well CF population and in a post modulator era?

0 0

Are large epidemiological study considerations relevant to what is quite a rare disease?

0 0

Machine learning models may be more accurate but are they widely useable?

1 0 2

CF specific measures

Could this call for more research into CF specific options for analysis of CF data? For example there are recent data creating CF specific PA thresholds, but these are restricted to paediatric groups. Do we need more research into this to have confidence in how we analyse accelerometer data in CF?

1 0

Why do we *need* cut points derived from people with CF?

0 0

Well done, clear, comprehensive, agree with conclusions.

5 0 1

Unpublished refs

Not sure if it's ok to include unpublished refs???
If the one under review is accepted before this consensus document is submitted, great, but have concerns about including a completely unpublished manuscript.

1 0 1

I like how the position statement has pushed for objective assessment of PA, but this will not be available in every clinic. Is it worth toning down the statement?

0 0

I think for this section in particular and the document as a whole it may be beneficial to offer some recommendations on 'best practice' based on the evidence available. I understand this wasn't explicitly the aim of the document but I think we have a good opportunity to provide some recommendations if appropriate.

0 0 2

Clinimetric Properties

Understanding these is key to
a) which method of PA monitoring chosen
b) Understanding its benefits and limitations

1 0

Thanks for this detailed summary.

In the final paragraph, is it cut-points developed 'for' or 'from' people with CF? Does it need to be articulated that the CF specific cutpoints referenced 'recently developed' or 'being developed' or such like given as they are yet to be published?

For the final statement, might qualifying that CF-specific cut-points would be better, but don't entirely rule out accelerometry as it exists presently be helpful? eg. 'Accelerometers can provide accurate information regarding the volume and accumulation of PA, particularly when CF-specific processes are used, ...'

0 0

Good review, clear

0 0

Key Reference

ECFS Position statement on physical activity in CF - Bradley J et al.

Should include this as although outdated was a CF-specific point in time guide to what was available

1 0

Really Clear

Really easy to follow and clear.

1 0

---

in the statement can you start by stating Accelerometers provide.... rather thna Accelerometers can provide...as the use of "can" implies a certain element of doubt

0 0

Wearables

A sentence on the commercially available wearable technology that is being used by many patients and clinicians/researchers alike would be helpful

0 0

Overall I think this is really well written. It might be good to mention fitness wearables in this section as a measure of PA.

Also Bradley et al Motion sensors in CF (2010) might be a good reference to consider

0 0

o_w_tomlinson + 6 · 1m

3.2 Measurement of Exercise

MEASUREMENT OF EXERCISE

Annual review exercise testing is recommended by the Cystic Fibrosis (CF) Trust. Testing to date has focused on evaluating aerobic fitness, a key prognostic indicator. Tests available range from simple field tests, to comprehensive evaluations of aerobic exercise (dys)function – cardiopulmonary exercise testing (CPET). 'Field tests', although easy to perform are limited in the information they provide, whereas CPET, the 'gold standard' measure of aerobic fitness, is recommended as the first-choice exercise test by the European CF Society Exercise Working Group. CPET offers a precise cardiovascular, respiratory and metabolic evaluation of exercise capacity, including assessment of mechanism(s) of exercise limitation [1].

Available tests of aerobic fitness range from 'field' tests to comprehensive analyses of aerobic exercise (dys)function, e.g. CPET. Whilst anaerobic (e.g. Wingate) tests and evaluations of muscular fatigue/fitness are available.

There are numerous options for the measurement of exercise / functional capacity and/or exercise intolerance in those with Cystic Fibrosis (CF); the selection of which is most appropriate is dependent on i) participant-level factors, such as age, disease severity/progression and the presence of comorbidities which may represent a contra-indication to certain types or intensities of exercise; ii) centre-level factors, such as the availability of exercise equipment, cost and space; and iii) the purpose of conducting the test, for example as a general assessment of exercise capacity and function or seeking to identify a specific cause(s) of exercise intolerance. Given the profound effects of the recent advances in modulator therapies on the health and functional capacities of those with CF, exercise testing has arguably never been so important. These improvements do, however, have implications when considering the optimal exercise test, with more demanding tests, and associated verification phases, now potentially feasible and, indeed, advocated, in a wider range of participants. For a comprehensive review of the exercise testing toolkit available for those with CF, readers are directed to the ECFS Exercise Working Group review [2].

Alternative, or complementary, exercise tests to the incremental ramp test for which appropriate evidence is available regarding their validity, reliability and clinometric properties include modified shuttle test, the six minute walk test, three minute step test, modified step test and one minute sit-to-stand test [2]. These field-based tests are less expensive and more portable but, consequently, provide less insight to exercise responses and the underlying cause(s) for exercise intolerance. Nonetheless, they should not be discounted as providing useful indications of functional ability, especially with regard to more subjective markers such a perceived exertion or dyspnoea.

Position Statement:
There are many safe, effective and informative options for (functional) exercise testing in those with CF regardless of age or disease severity; lab-based tests potentially provide greater insights but the value of field-based tests should not be discounted, especially with regard to the assessment of more subjective outcomes.

REFERENCES

1. Urquhart, D.S. and Z.L. Saynor, *Exercise testing in cystic fibrosis: Who and why?* Paediatric Respiratory Reviews, 2018. **27**: p. 28-32.
2. Saynor, Z.L., et al., *Multimodal exercise testing in cystic fibrosis: translating research into more standardised global clinical practice.* In Preparation.

0 0

It may be important to identify which field tests you are referring to

2 0

Field tests are limited but do provide clinically valuable information

0 1 1

muscular evaluation too?

1 0

This short para could be removed, as some of the content is already stated above?

4 0

Overall, you make the case that CPET is the best, which I agree. However, the argument that field tests "should not be discounted" is not supported by literature. It would be good to include some of the literature demonstrating the benefits of the "field tests" to align with the Position Statement. IF oyu need space, a lot can be cut out of the middle section.

3 1 2

Sturcute

I wonder if the statement should be divided into different fitness measures, as currently the focus is mostly aerobic:
Aerobic
Anaerobic
Strength

3 0

The title does not align with the content which may explain the confusion. Is this looking at the measurement of exercise capacity (what is discussed) or the measurement of exercise as a discrete component of physical activity (what the title implies?)

1 1

From Craig: could you look at this consensus statement again and perhpas think how it can be more active in its statement, what i am trying to elucidate is thta it is descriptive in tone - could it have a more proactive implication/meaning

0 0

More details needed on CPETs and the use of validation bouts to avoid issues with submaximal efforts. Also, what about other lab-based tests such as constant work rate tests or submaximal parameters determined from a ramp test? There is a lot of recent work looking at OUES for example

0 0

May want to make these 2 different statements

0 0 1

It would be great to see more comprehensive referencing within this section, including the ERS and ECFS Working Group statements on exercise testing.

6 0

o_w_tomlinson + 7 · 2mo

4.1 Optimal Training

OPTIMAL TRAINING MODES AND STYLES

The *optimal* mode of exercise training for people with CF remains under investigation and largely depends on the goals of the patient and clinician. There is conflicting evidence from RCTs that regular continuous aerobic exercise training undertaken at a moderate intensity, and strength training can elicit improvements in lung function (FEV_1) in adolescents and adults with CF (1), and strong evidence that aerobic training elicits improvements in exercise capacity. Strength training alone is unlikely to be sufficient to produce improvements in exercise capacity, particularly in trained adults and children (2). Though the reasons for participating in regular exercise training are multifactorial, the most noteworthy for the patient may be to improve maximal exercise capacity, due to associations between this measure and mortality in people with CF (3).

Numerous RCTs have investigated modes of aerobic exercise of ~30 to 60 minutes of walking, running, cycling or mixed exercise at a moderate intensity or higher (i.e. 50% of VO_{2peak} or 60 to 85% of peak heart rate) (4). Habitual physical activity, including light intensity exercise, is unlikely to produce sufficient benefits in exercise capacity (5), though further investigation of the benefits of habitual/light intensity exercise in people with CF may be warranted.

Preliminary data supports the tolerability, feasibility and initial effectiveness of interval-based training (6–9). This mode may be optimal compared to continuous moderate intensity aerobic exercise in people with CF in circumstances where a person is unable to sustain continuous exercise for a sufficient length of time to elicit physiological adaptions in skeletal muscle (i.e. those with severe respiratory disease) (7). Specifically, high intensity interval training (HIIT) may reduce the total exercise time, as people are able to achieve a higher total work intensity than they may otherwise be able to achieve during continuous exercise training (8). The first case study undertaken in this area prescribed a training frequency of thrice weekly for 6 weeks in a young female with CF. Each training session consisted of 10 to 20 intervals involving 30 seconds of high intensity exercise (50 to 90% maximal exercise capacity) interspersed with a 60 second recovery period (25%). One recent small RCT investigated the effects of 45 minutes of biweekly interval-based exercise for 8 weeks (work intervals at 70% of peak work rate interspersed with 60 seconds of recovery at 35%) (9). Another recent small RCT in adults investigated the effects of 8 weeks of low-volume HIIT comprising 3 sessions per week and 10 minutes per session (1 minute of symptom limited work intervals interspersed with 1 minute of active recovery; 2-minute warm-up and cool-down) (8). Supervised interval-based training may be considered in the inpatient (7), outpatient (8) and community-based setting (6).

Comprehensive routines may also include exercises aimed at optimising bone mineral density (10), for example, those with load bearing, plyometric components (11).

Considering the evidence available in this area, the most *optimal* mode of exercise training for people with CF is individually prescribed, varied and enjoyed in order to maximise long-term patient adherence.

Position Statement: Structured aerobic exercise training, undertaken at a moderate intensity or higher as part of the ongoing therapeutic routine, is likely to offer optimal improvements in exercise capacity and other important health outcomes in most people with CF, compared to lower intensity aerobic exercise or strength training alone, though a well-rounded, comprehensive training program (including aerobic, strength and other training) is desirable.

REFERENCES

1. Kriemler S, Kieser S, Junge S, Ballmann M, Hebestreit A, Schindler C, Stüssi C, Hebestreit H. Effect of supervised training on FEV1 in cystic fibrosis: a randomised controlled trial. J Cyst Fibros. 2013 Dec;12(6):714-20. doi: 10.1016/j.jcf.2013.03.003. Epub 2013 Apr 13. PMID: 23588193.
2. Orenstein DM, Hovell MF, Mulvihill M, Keating KK, Hofstetter CR, Kelsey S, Morris K, Nixon PA. Strength vs aerobic training in children with cystic fibrosis: a randomized controlled trial. Chest. 2004 Oct 1;126(4):1204-14.
3. Hebestreit H, Hulzebos EH, Schneiderman JE, Karila C, Boas SR, Kriemler S, Dwyer T, Sahlberg M, Urquhart DS, Lands LC, Ratjen F. Cardiopulmonary exercise testing provides additional prognostic information in cystic fibrosis. American journal of respiratory and critical care medicine. 2019 Apr 15;199(8):987-95.
4. Radtke T, Nevitt SJ, Hebestreit H, Kriemler S. Physical exercise training for cystic fibrosis. Cochrane Database of Systematic Reviews. 2017(11).
5. Hebestreit H, Arets HG, Aurora P, Boas S, Cerny F, Hulzebos EH, Karila C, Lands LC, Lowman JD, Swisher A, Urquhart DS. Statement on exercise testing in cystic fibrosis. Respiration. 2015;90(4):332-51.
6. Hulzebos HJ, Snieder H, van der Et J, Helders PJ, Takken T. High-intensity interval training in an adolescent with cystic fibrosis: a physiological perspective. Physiotherapy theory and practice. 2011 Apr 1;27(3):231-7.
7. Gruber W, Orenstein DM, Braumann KM, Beneke R. Interval exercise training in cystic fibrosis—effects on exercise capacity in severely affected adults. Journal of Cystic Fibrosis. 2014 Jan 1;13(1):86-91.
8. Sawyer A, Cavalheri V, Jenkins S, Wood J, Cecins N, Bear N, Singh B, Gucciardi D, Hill K. High-Intensity Interval Training Is Effective at Increasing Exercise Endurance Capacity and Is Well Tolerated by Adults with Cystic Fibrosis. Journal of clinical medicine. 2020 Oct;9(10):3098.
9. Reuveny R, DiMenna FJ, Gunaratnam C, Arad AD, McElvaney GN, Susta D, Peled M, Moyna NM. High-intensity interval training accelerates oxygen uptake kinetics and improves exercise tolerance for individuals with cystic fibrosis. BMC Sports Science, Medicine and Rehabilitation. 2020 Dec;12:1-3.
10. García ST, Sánchez MA, Cejudo P, Gallego EQ, Dapena J, Jiménez RG, Luis PC, de Terreros IG. Bone health, daily physical activity, and exercise tolerance in patients with cystic fibrosis. Chest. 2011 Aug 1;140(2):475-81.
11. Gupta S, Mukherjee A, Lodha R, Kabra M, Deepak KK, Khadgawat R, Talwar A, Kabra SK. Effects of exercise intervention program on bone mineral accretion in children and adolescents with cystic fibrosis: a randomized controlled trial. The Indian Journal of Pediatrics. 2019 Nov;86(11):987-94.

0 0 · 0

This seems to have a lot of overlap with other sections, perhaps this could be a shorter summary referring to the evidence presented in previous sections?

0 0 · 0

Habitual/light

Do you think this cold be more viable in patients with more severe CF?

1 0 · 0

HIIT vs other forms?

Are there any data comparing HIIT vs. other types of training in CF (i.e continuous)?

0 0 · 1

Use of optimal in the statement.

Should this be greater rather than optimal?

I hope this and my above comments are useful - really enjoyed reading this. Thank you.

2 0 · 0

The other summaries do not convey the notion for strong evidence to improve exercise capacity - will need to make sure the messaging is consistent. The fitness summary terms this as 'some evidence'. I guess this will depend on what framework we decide to use to grade evidence?

1 0 · 0

"Considering the evidence available in this area..." - agree with this point but don't think the evidence above supports that statement, could you provide a reference for it?

1 0 · 0

Thank you. I like the position statement and believe it is support by the literature - which is summarised well. Did you consider a statement on severe/ limited patients. I believe there's good evidence for the interval training approaches in this group

0 0 · 0

Optimal?

I wonder if we should use the term optimal in the title? This would be very hard to pin down. Should the heading be titled 'Training modes and styles'?

2 0 · 1

I agree with this comment, I totally agree with the statement but it is not linked to the evidence above.

1 0 · 0

Is it possible to comment on the strength of the evidence in the positional statement?.

0 0 · 2

I think the issue is always "optimal" for what and this should be made clear

0 0 · 0

o_w_tomlinson ✦ 10 ● 1m

4.2 Improving Adherence

ADHERENCE

A key finding from the evidence is the generally low uptake of physical activity among children and young people which is also reflected among those living with cystic fibrosis. There are a variety of factors that influence engagement in physical activity and adherence to recommendations that are similar to healthy peers, but there are some that are specific to those living with Cystic Fibrosis.

Education about the benefits of exercise
In promoting a lifestyle that incorporates regular physical activity education about the physical, mental, psychological and health benefits is key to success. Professor David Orenstein is a believer in leading from the front. He is of the opinion that CF centres where the members of the team lead exercise regularly themselves are more likely to motivate pwCF to engage in regular physical activity.

Some of the strongest arguments for regular exercise in cystic fibrosis are the anti-inflammatory effects and immune cell activation associated with reduced disease incidence and viral infection susceptibility. To achieve these outcomes the recommendation is regular exercise of moderate intensity and duration as opposed to too little or too much exercise. Educating patients about finding their "sweet spot" on the bell shaped curve of duration, intensity (using HR for age information) and frequency have been found to be motivating with adults with and without CF. The Fox and Haskell Formula presented to pwCF in a coloured A4 page chart assists in establishing in a collaborative way establishing the best personalized exercise program.

Identifying enablers and barriers – a personalised collaborative approach
Part of the process of encouraging pwCF to engage in regular exercise is a assisting them in identifying their enablers and barriers. Everyone finds tracking devices useful in terms of how much they are actually walking or running in daily life. Smart watches, Smart phones in a pocket, and many other wearable tracking devices are currently available. Many of our pwCF already own one of these. Not all are aware of the tracking Apps that are freely available or already on their phones – helping them set them up during a consultation can be a great enabler. Incidental exercise should be considered as many children and adults are achieving their goals during their daily life at work or school and should be commended for this achievement. Tracking devices even for one usual weekday and one usual weekend day will give valuable insight into how much or little activity is occurring.

In counselling people with CF to establish and maintain a regular exercise program an individualized or personalised approach is essential. Using a motivational interviewing type approach is more likely to elicit engagement in the process compared to a lecturing, nagging, authoritarian, prescriptive approach. Motivational interviewing (MI) is a counselling method that involves enhancing a patient's motivation to change by means of four guiding principles: resisting the righting reflex, understand the patient's own motivations; listen with empathy and empower the person. Within MI the therapist is viewed as a facilitator rather than an expert, who adopts a nonconfrontational approach to guide the patient towards change. The overall spirit of MI has been described as collaborative, evocative and honouring of patient autonomy.

Creating opportunities to be active and develop a regular routine
Within the context of living with cystic fibrosis, time is precious with a range of competing priorities vying for the same bit of limited availability of "spare time". Opportunities could be created to combine physical activity with other valued activities – removing the need to choose between one or the other. For example, doing something active with friends or family, or making friends in a team sport or exercise class.

By bringing in the social aspects of physical activity, the activity is more likely to be perceived as enjoyable, which in turn facilitates ongoing engagement in the activity. Another other opportunity would be to consider active travel to school, work, or other destinations, removing the need to find additional time for physical activity.

In the moment decisions about engaging in physical activity may require motivation to overcome specific barriers at that time. Building up healthy habits by introducing a regular routine of physical activity, reduces the need for relying on motivation as the behaviour becomes more automatic. Habit formation requires consistent repetition of an action in the same context. This may take some planning in advance, over time this requires much less effort than actively motivating yourself to do something. To make a new healthy activity habit.

1. Set on a goal.
2. Choose an activity.
3. Plan when and where to do this activity.
4. Every time you get to that time and place, do the activity.
5. By being consistent, it will get easier with time. You'll end up doing it automatically without even having to think about it.
6. There is no single way in which children and young people should be active; The focus should be on identifying activities that they find enjoyable, and on creating opportunities to be active.

"Exercise is medicine" (USA) projects negative connotations and feelings. A more inspiring and motivating mantra - "Exercise is the elixir of life".

REFERENCES
Pauline Barbera van de Weert-va Leeuwen, Hubertus Gerardus Maria Arets, Cornelius Korstiaan van der Ent, Jeffrey Matthijn Beekman. Infection, inflammation and exercise in cystic fibrosis. Respir Res 2013, 14(1): 32. Published online 2013 Mar 6 doi: 10.1186/1465-9921-14-32.

0 0

---

citation here?
1 0

'among children and young people' does this mean not adults?? this is how it reads, what about our older population?
2 0

There is repetition in paragraph 3 with previous sections - suggest omitting the argument about why people with CF should exercise as they have already been covered.
1 0

needs a reference in this first statement in the first paragraph
0 0

Is Prof Orensteins point personal opinion or evidenced based? Think we need to stick to evidence for this document
5 0

< I agree with this point - need to provide evidence
1 0

The benefits of PA and exercise are discussed throughout. This section could be limited to adherence
1 0

I don't think we can recommend only 1-2 days monitoring -that doesn't provide valid information at all. Need at least 4days (ideally 3 Mon-Fri and 1 Sat-Sun)
2 0 1

Some of the statements in the 'identifying enablers and barriers' section includes some anecdotal / sweeping comments (i.e. everyone finds tracking devices useful). Are there any papers in CF or other chronic disease that you could draw evidence from to support these statements?
2 0

Thank you for this overview on strategies to support improving adherence to physical activity/exercise.

Paragraph 2 sentence 2: I think the word 'lead' between 'team' and 'exercise' may be extraneous.

Paragraph 4 - would it be clearer if the concept of 'time is precious' is placed in the context of PwCF ie. PwCF identify that they are time poor/their time is precious?

I think it might be helpful for the reader for more references to be supplied - particularly where key details are indicated eg. Fox and Haskell Formula, MI etc. Similarly, is there any patient reported data that confirms desire to use wearables/tracking devices that could be included?

I wasn't clear if the sentence containing the two quotes was the summary statement.
1 0

The evidence to support the use of motivational interviewing should be discussed and a citation provided
1 0

This reads more like an opinion piece than a summary of the literature. There are loads of studies investigating adherence - S/R by Cox, plus dozens of qualitative studies identifying barriers and facilitators. These need to be included in this summary.
4 0

References
Only one reference has been included. There is a lot of literature investigating adherence to treatments etc in CF and this needs to be included eg

- DOI: 10.1002/ppul.10126

2 0

More references needed throughout
4 0

Overall there needs to be a stronger reflection back to evidence within the abstract. And a evidence based statement made at the end
3 0

Has this Fox and Haskell formula been validated and tested extensively?
0 0

There is some evidence to suggest that activity monitors can be used as motivation tools but I don't think it can be claimed that 'everyone finds tracking devices useful...'
2 0

Could you provide a reference for Dr Orienstien please
0 0

I agree with the latter list of option to make PA habit, but this is not the purpose of synthesising the evidence. The last sentence is just a conjectural stateemnt. We need a consensus statement that summs up an aspect fo adherence research for people with Cf and PA/exercise
0 0

padlet

o_w_tomlinson + 7 1m

4.3 Staffing

STAFFING IN CLINICAL PRACTICE

Physical activity (PA) and exercise are integral to the overall management of individuals with CF, as such it is recommended that CF services should include the assessment of exercise capacity, the prescription and monitoring of exercise programmes, PA education, support and promotion in both in-patient and out-patients settings, irrespective of age and disease severity [1][2][3]. The responsibility for delivering such services is typically absorbed by CF physiotherapy services [1][4].

There are currently no guidelines for the staffing or training requirements for the provision of exercise in CF care. To perform the gold standard exercise testing recommended annually for individuals with CF, CPET, it is recommended that two members of staff are present, with at least one properly trained and experienced to perform the test, recognise adverse events, respond to emergencies and be aware of CF specific infection control guidelines [5]. Standard physiotherapy training does not currently include conducting or interpreting CPETs, thus highlighting a requirement for CPD opportunities for physiotherapists in this area and/or the potential role of clinical exercise physiologists in CF care.

A recent audit of physiotherapy duties in an Australian CF clinic revealed that only 13% of the total workload undertaken by physiotherapists is dedicated to exercise [6]. Exercise prescription is not typically included as part of physiotherapists' training. As such, additional training should be available for CF specialist physiotherapists to provide such services, alternatively exercise professionals could be employed within the CF MDT to deliver these services. In those areas where CPET is not available, the delivery of alternative exercise testing and the prescription and monitoring of exercise programmes could be undertaken by appropriately trained and experienced exercise professionals.

There is an increasing presence of exercise professionals working in health care and although training, roles, responsibilities and titles vary internationally there are now accreditation programmes available for clinical exercise physiologists in the United States [7], Canada [8] and Australia [9]. Clinical exercise physiologists are defined as "allied health professionals specialising in the delivery of scientific exercise interventions for people with acute, subacute, or chronic medical conditions across a wide spectrum of health, including but not limited to cardiovascular, respiratory, endocrine, musculoskeletal, mental and neurological disease" [10]. Whilst there are examples of accredited clinical exercise physiologists working as independent practitioners with clinical populations there are few examples of this in CF care. Similar accreditation programmes are not yet available in the United Kingdom or Europe although there are examples of exercise professionals working as physiotherapy assistants or in similar roles [11]. The educational, training and experience requirements for clinical exercise physiologists working in CF are not yet standardised. Similarly, the roles, responsibilities and competency requirements remain largely undefined. Such roles will likely require a degree level qualification in sports and exercise sciences or a related field and where possible accreditation and registration with an appropriate body upholding standards of care.

Based on the current recommendations for physiotherapy staffing requirements in CF services [4] experience and expert opinion it is feasible that a full-time (1.0 whole-time equivalent [WTE]) AHP such as an appropriately trained and experienced 'Clinical Exercise Physiologist' could provide exercise services for cohorts of ~150 patients. There may be scope for individuals with lower banding, such as exercise professionals without an undergraduate degree (e.g. 'exercise technician', akin to a 'support worker') to assist a full-time individual in larger centres (~250 patients), and it is likely that additional exercise support (0.5 WTE) is necessary for every increase of 75 patients thereafter in centres with more than 250 patients. In smaller centres (~75 patients) the provision of exercise could feasibly be delivered by an exercise professional on a 0.5.WTE contract or by an appropriately trained and experienced physiotherapist.

Position Statement: The provision of exercise within CF care is becoming increasingly important and requires additional staffing and expertise, therefore efforts should be made to standardise education, training and the roles and responsibilities of clinical exercise physiologist working in CF and/or to provide CPD opportunities for CF physiotherapists wishing to develop expertise in exercise provision.

REFERENCES

[1] National Institute for Health and Care Excellence (NICE), "Cystic fibrosis: diagnosis and management guideline. www.nice.org.uk/guidance/ng78," no. October 2017, 2017.

[2] C. Castellani *et al.*, "ECFS best practice guidelines: the 2018 revision," *J. Cyst. Fibros.*, vol. 17, no. 2, pp. 153–178, 2018.

[3] B. M. Button *et al.*, "Physiotherapy for cystic fibrosis in Australia and New Zealand: A clinical practice guideline," *Respirology*, vol. 21, no. 4, pp. 656–667, 2016.

[4] Cystic Fibrosis Trust, "Standards of Care and Good Practive for the Physiotherapy Management of Cystic Fibrosis (2020)," no. November, pp. 160–162, 2020.

[5] H. Hebestreit *et al.*, "Statement on exercise testing in cystic fibrosis," *Respiration*, vol. 90, no. 4, pp. 332–351, 2015.

[6] K. Hall *et al.*, "Benchmarking service provision, scope of practice, and skill mix for physiotherapists in adult cystic fibrosis care delivery," *Physiother. Theory Pract.*, 2020.

[7] A. H. Bowersock, W. A. Breeding, and C. A. Sheppard, "Hiring Practices of Exercise Physiologist in Cardiac Rehabilitation Programs among Mid-Atlantic States in the United States," *J. Clin. Exerc. Physiol.*, vol. 5, no. 3, pp. 32–36, 2016.

[8] D. E. R. Warburton, S. A. Charlesworth, H. J. A. Foulds, D. C. McKenzie, R. J. Shephard, and S. S. D. Bredin, "Qualified exercise professionals: Best practice for work with clinical populations," *Can. Fam. Physician*, vol. 59, no. 7, pp. 759–761, 2013.

[9] N. A. Smart, A. Williams, and K. Lyndon, "The Role and Scope of Accredited Exercise Physiologists in the Australian Healthcare System," *J. Clin. Exerc. Physiol.*, vol. 5, no. 2, pp. 16–20, 2016.

[10] A. Pearce and G. Longhurst, "The role of the clinical exercise physiologist in reducing the burden of chronic disease in new zealand," *Int. J. Environ. Res. Public Health*, vol. 18, no. 3, pp. 1–13, 2021.

[11] O. W. Tomlinson, J. Shelley, S. Denford, A. R. Barker, P. J. Oades, and C. A. Williams, "Promotion of exercise in the management of cystic fibrosis - summary of national meetings," *Eur. J. Pers. Centered Healthc.*, 2018.

0 0

---

incorporated instead of absorbed?

0 0

Comment

The last sentence in paragraph 5 doesn't read right to me. It seems to be saying that an experienced and trained physiotherapist could only deliver exercise services in a smaller centre? Do you mean that as it's a smaller centre it could be part of a wider caseload? Might be worth re-wording.

Also might be worth mentioning the complementary roles that physiotherapists and exercise practitioners can have working together. At the moment it sounds a little like you can only have one or the other...

1 0

Thank you. I wonder in the last paragraph if it might be better to just say "appropriate AHP". Titles are so different around the world.

0 0

Think the wording needs to be careful in terms of

0 0

I would have said that exercise prescription is commonly included in physiotherapist undergrad training

2 0 5

3rd paragraph, last sentence I agree the exercise prescription and training could be sent out to other professionals but how likely is the actual testing, particularly if it is to be used for clincial purposes? I am assuming this comment is in relation to some exercise trainers getting involved with the Cf community in offering exercise and fitness classes outside of the hospital?

0 0

I like this level of technical staff detail in the 5th paragraph - makes it tangible

1 0

To perform the gold standard...." is a long sentence with a couple of themes in suggest break into two sentences

0 0

1d

0 0

22m

0 0

22m

0 0

22m

0 0

Translating exercise test results into counselling/advice

I feel that this concept warrants a sentence/paragraph

0 0

I wonder in the statement behind the clincial exercise physiologist in brackets we should have something like (or their equivalents) to take account of different worldwide titles?

0 0

Think the wording needs to be careful in terms of staffing. This doc suggests that exercise testing only carried out by a physiologist and that most physiotherapists (In australia anyway) don't really dedicate much time to exercise. However, I don't think this is the case in every centre. I know in ours it is the physiotherapist that does exercise testing and also exercise prescription so therefore think wording needs to allow for that

0 0

Thanks for this clearly written statement. A couple of thoughts on reading: Do we need to make the language more inclusive - eg. a north american audience would associate with physical therapist/respiratory therapist - and the relevant service provision? Similarly reference to position 'banding'? And in that vein, might the summary statement be more inclusive if 'efforts should be made to standardise education, training, roles and responsibilities for healthcare professionals involved in the prescription, supervision and monitoring of exercise programs/services for people with CF' (ie. not limited to specific disciplines).

I wonder if there needs to be a caveat in the suggestion around training/expertise to conduct CPET - in some jurisdictions all the training in the world will still not 'authorise' a physiotherapist to be able to conduct a CPET.
In the final paragraph AHP has not been previously defined.

I think the point around diversifying the expertise within a CF team/centre to provide such services is well made. I do think there might be plenty of physiotherapists who would disagree about their lack of training/expertise to prescribe exercise, so wording will likely be important.

I wonder if additional background that underpins the suggested time fractions relative to caseload would be worthwhile? It is likely such a document may be used in future to support/lobby for staff acquisition.

2 0

o_w_tomlinson ✦ 5 ● 1m

4.4. Telehealth

TELEHEALTH AND ACTIVITY AND EXERCISE IN CYSTIC FIBROSIS

Telehealth is the delivery of care via any electronic means when the patient and healthcare professional are separated by distance. This encompasses multiple modalities, including telephone and video-calls, emails, and text messaging, to support diagnoses, monitoring and therapeutic interventions [1]. To date, use of telehealth has been limited in CF, for example, it has been utilised for remote consultations [2], monitoring for detection of exacerbations [3] and preparation for transplantation [4]. The application of telehealth in CF has been systematically reviewed once [5], although heterogeneity in the interventions implemented and outcomes used make firm conclusions difficult to draw on the efficacy of telehealth.

In relation to exercise testing, telehealth has been utilised to remotely monitor 3-minute step tests, finding no difference in outcomes when compared to tests completed in person [6]. In relation to exercise training, telehealth has been utilised to engage children [7] and adults [8,9] in instructor-led training, either through their own clinical team [8] or third-party providers [9]. Moreover, telehealth has been utilised to engage adults with CF in physical activity via a novel website [10]. These studies have, for the most part, been single-group feasibility studies with relatively small numbers of participants ($n \leq 10$) and therefore differences in function are either not reported using conventional statistics [7,8], or show no statistically significant differences [10]. The one trial to compare a home-based telehealth programme versus a hospital-based programme showed no differences between groups, although a small sample size, high withdrawal and heterogeneity in function due to severe disease status makes true effects difficult to establish [9]. Finally, further use of telehealth to deliver exercise sessions has also been reported, but not peer-reviewed [11,12], and therefore findings cannot be confidently utilised.

Whilst these studies have yet to establish a significant benefit to telehealth, encouragingly these studies reveal high acceptance of, and desirability for, telehealth [7,8,10] as well as increased adherence relative to hospital-based regimens [9]. Only a small number of adverse events have been reported, albeit in a group of people with severe lung disease who were listed for transplant [9]. This therefore indicates remote delivery of exercise is indeed feasible and worthy of further consideration. Currently, randomised control trials are ongoing to the impact of remote physical activity promotion [13], physiotherapy consultations [14] and activity monitoring [15] upon parameters of fitness and activity, although results have yet to be reported.

Finally, it should be noted that the role of telehealth has been predominantly investigated prior to the global COVID-19 pandemic, and this public health crisis has brought about rapid change in overall acceptability and use of telehealth platforms. Initial surveying of clinical teams in the UK suggests that use of telehealth to deliver exercise training will continue as part of standard practice following the pandemic [16], and it is therefore how this modality of healthcare delivery will be adapted and implemented in the future is worth of consideration by clinical teams.

Position Statement: Clinical efficacy of exercise delivered by digital means is currently unclear, but it has been shown to be feasible and acceptable to patients with cystic fibrosis, and clinical teams should be encouraged to implement its use.

REFERENCES
1 Shaw DK. Overview of Telehealth and Its Application to Cardiopulmonary Physical Therapy. Cardiopulmonary Physical Therapy Journal 2009;20:13–8.
2 Wood J, Mulrennan S, Hill K, et al. Telehealth clinics increase access to care for adults with cystic fibrosis living in rural and remote Western Australia. Journal of Telemedicine and Telecare 2017;23:673–9. doi:10.1177/1357633X16660646
3 Wood J, Jenkins S, Putrino D, et al. A smartphone application for reporting symptoms in adults with cystic fibrosis improves the detection of exacerbations: Results of a randomised controlled trial. Journal of Cystic Fibrosis Published Online First: 12 September 2019. doi:10.1016/j.jcf.2019.09.002
4 Wilkinson OM, Duncan-Skingle F, Pryor JA, et al. A feasibility study of home telemedicine for patients with cystic fibrosis awaiting transplantation. Journal of Telemedicine and Telecare 2008;14:182–5. doi:10.1258/jtt.2008.070107
5 Cox NS, Alison JA, Rasekaba T, et al. Telehealth in cystic fibrosis: a systematic review. Journal of Telemedicine and Telecare 2012;18:72–8. doi:10.1258/jtt.2011.110705
6 Cox NS, Alison JA, Button BM, et al. Assessing exercise capacity using telehealth: a feasibility study in adults with cystic fibrosis. Respiratory Care 2013;58:286–90. doi:10.4187/respcare.01922
7 Chen JJ, Cooper DM, Haddad F, et al. Tele-Exercise as a Promising Tool to Promote Exercise in Children With Cystic Fibrosis. Frontiers in Public Health 2018;6. doi:10.3389/fpubh.2018.00269
8 Tomlinson OW, Shelley J, Trott J, et al. The feasibility of online video calling to engage patients with cystic fibrosis in exercise training. Journal of Telemedicine and Telecare 2020;26:356–64. doi:10.1177/1357633X19828630
9 Layton AM, Irwin AM, Mihalik EC, et al. Telerehabilitation Using Fitness Application in Patients with Severe Cystic Fibrosis Awaiting Lung Transplant: A Pilot Study. International Journal of Telemedicine and Applications 2021;2021:e6641853. doi:10.1155/2021/6641853
10 Cox NS, Alison JA, Button BM, et al. Feasibility and acceptability of an internet-based program to promote physical activity in adults with cystic fibrosis. Respiratory Care 2015;60:422–9. doi:10.4187/respcare.03165
11 Hillen B, Pfirrmann D, Simon P, et al. P366 A 12-week, individualised, web-based exercise intervention is feasible and effective for people with cystic fibrosis. Journal of Cystic Fibrosis 2019;18:S161. doi:10.1016/S1569-1993(19)30658-7
12 Milligan CM, Pollard K, Watson R, et al. P86 Physiotherapist-led online exercise session for people with cystic fibrosis (CF) during the COVID-19 pandemic: a service evaluation. Thorax 2021;76:A134–A134. doi:10.1136/thorax-2020-BTSabstracts.231
13 Cox NS, Eldridge B, Rawlings S, et al. A web-based intervention to promote physical activity in adolescents and young adults with cystic fibrosis: protocol for a randomized controlled trial. BMC Pulmonary Medicine 2019;19:253. doi:10.1186/s12890-019-0942-3
14 Lang RL, Wilson C, Stockton K, et al. CyFiT telehealth: protocol for a randomised controlled trial of an online outpatient physiotherapy service for children with cystic fibrosis. BMC Pulmonary Medicine 2019;19:21. doi:10.1186/s12890-019-0784-z
15 Raywood E, Douglas H, Kapoor K, et al. Protocol for Project Fizzyo, an analytic longitudinal observational cohort study of physiotherapy for children and young people with cystic fibrosis, with interrupted time-series design. BMJ Open 2020;10:e039587. doi:10.1136/bmjopen-2020-039587
16 Tomlinson OW, Saynor ZL, Stevens D, et al. The impact of COVID-19 upon the delivery of exercise services within cystic fibrosis clinics in the United Kingdom. MedRxiv Published Online First: 16 April 2021. doi:10.1101/2021.04.12.21255205

1 0

what is a firm conclusion?

0 0

Should Pacster and CF Beam be discussed within this section?

0 0 1

Wording adjustment '.. to investigate the impact of remote physical activity promotion...'

0 0

Final paragraph, this sentence is too long, can you please break it into two

0 0

Very well written piece

4 0

Thanks for this clear summary.
In paragraph 2 it might be useful to indicate the type of program being referred to in the hospital versus telehealth comparison ie. was it exercise training, PA promotion etc. In the last sentence of paragraph 2 I would delete the word 'further'.

Paragraph 3 - I wonder if it is worth specifically articulating that the improved adherence to hospital-based programs is in one study only (this is clearly implied as written to, but I wonder if it should be obvious) in light of adherence rates to remote programs/monitoring being widely variable (and not always fabulous) (as indicated in the systematic review, and I think in more recent publications).

I think the summary statement is clear. I would suggest that the final sentence be 'clinical teams should be encouraged to consider its use' rather than implement, given that you've indicated the efficacy is unclear.

References are comprehensive.

2 0

o_w_tomlinson ✦ 12 ● 1m

5.1 Airway Clearance

EXERCISE FOR AIRWAY CLEARANCE

Daily airway clearance treatments (ACTs), such as the active cycle of breathing technique, autogenic drainage and the use of positive expiratory pressure devices, are one of the cornerstones in the management of CF lung disease [1]. There is widespread agreement among people with CF and healthcare professionals that exercise may also improve airway clearance [2] and many people with CF already substitute traditional ACTs with exercise [3]. Whether or not exercise is a satisfactory substitute for traditional ACTs in people with CF has been identified as a top 10 research priority [4]. Adults with CF spend on average nearly one hour per day on ACTs and exercise regimens [5]. If exercise could adequately replace traditional ACTs for people with CF, it may also reduce treatment burden, another of the top 10 research priorities [4].

A recent systematic review, which included 12 studies of 187 children and adults with CF, investigated the effects of exercise on airway clearance compared to no intervention and compared to traditional ACTs [6]. All except one study were randomised cross-over trials with small sample sizes (n≤32) and short duration (ranging from a single-session up to two weeks), so there were no data for longer term outcomes such as exacerbation frequency and quality of life. Due to significant heterogeneity of the exercise and ACTs, however, meta-analyses were limited. Exercise compared to no intervention resulted in trends or significant improvements in mucus clearance and expectorated sputum weight [7-9]. When exercise was compared to traditional ACTs, there were distinct differences in efficacy if the exercise did or did not include encouraged huff or cough. All studies that did not include huff or cough reported significantly less mucus clearance or expectorated sputum volume compared to the traditional ACT [8, 10-12]. Whereas all studies that did include huff or cough reported no significant difference in mucus clearance or expectorated sputum volume compared to the traditional ACT [13-17]. It is likely, however, that some of the studies were underpowered, so the review cannot exclude small differences between exercise and traditional ACTs that may not have been detected.

The clinical implications are to recommend including huff or cough with exercise if intending to improve airway clearance and that it is possible a single session of exercise (with huff or cough) may have similar effects as traditional ACTs. There is no evidence, however, to answer the question whether or not exercise can act as a substitute for traditional ACTs in the medium or long term, as none of the included studies had a duration of more than two weeks. That highly relevant clinical question will only be answered with a long-term randomised controlled non-inferiority trial comparing exercise to traditional ACTs with meaningful outcomes, such as exacerbation frequency and quality of life. There is interest and good will to investigate this topic, as a recent survey reported 48% of people with CF skip their ACT if they have exercised and 73% of healthcare professionals would support a trial of this design [2].

Position Statement: Exercise with huff or cough improves mucus clearance, however there is no medium or long-term evidence to answer the question if exercise can adequately replace ACTs in people with CF.

REFERENCES

1. International Physiotherapy Group for Cystic Fibrosis. Physiotherapy for people with cystic fibrosis: From infant to adult, Kerstan M and Maguire I, Editors. 2019; IPG/CF.
2. Rowbotham NJ, Smith SJ, Davies G, Daniels T, Elliott ZC, Gathercole K, Rayner OC, Smyth AR. Can exercise replace airway clearance techniques in cystic fibrosis? A survey of patients and healthcare professionals. Journal of Cystic Fibrosis 2020; 19(4): e19-e24.
3. Ward N, Stiller K, Holland AE, and the Australian Cystic Fibrosis Exercise Survey group. Exercise is commonly used as a substitute for traditional airway clearance techniques by adults with cystic fibrosis in australia: A survey. Journal of Physiotherapy 2019; 65(1): 43-50.
4. Rowbotham NJ, Smith S, Leighton PA, Rayner OC, Gathercole K, Elliott ZC, Nash EF, Daniels T, Duff AJA, Collins S, Chandran S, Peaple U, Hurley MN, Brownlee K, Smyth AR. The top 10 research priorities in cystic fibrosis developed by a partnership between people with cf and healthcare providers. Thorax 2018; 73(4): 388-390.
5. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: Challenges to disease self-management. Journal of Cystic Fibrosis 2009; 8(2): 91-96.
6. Ward N, Morrow S, Stiller K, Holland AE. Exercise as a substitute for traditional airway clearance in cystic fibrosis: A systematic review. Thorax 2020; epub ahead of print: thoraxjnl-2020-215836.
7. Baldwin DR, Hill AL, Peckham DG, Knox AJ. Effect of addition of exercise to chest physiotherapy on sputum expectoration and lung function in adults with cystic fibrosis. Respiratory Medicine 1994; 88(1): 49-53.
8. Dwyer TJ, Daviskas E, Zainuldin R, Verschuer J, Eberl S, Bye PTP, Alison JA. Effects of exercise and airway clearance (positive expiratory pressure) on mucus clearance in cystic fibrosis: A randomised crossover trial. European Respiratory Journal 2019; 53(4): 04.
9. Kriemler S, Radtke T, Christen G, Kerstan-Huber M, Hebestreit H. Short-term effect of different physical exercises and physiotherapy combinations on sputum expectoration, oxygen saturation, and lung function in young patients with cystic fibrosis. Lung 2016; 194(4): 659-664.
10. Bilton D, Dodd ME, Abbot JV, Webb AK. The benefits of exercise combined with physiotherapy in the treatment of adults with cystic fibrosis. Respiratory Medicine 1992; 86(6): 507-511.
11. Falk M, Kelstrup M, Andersen JB, Pedersen SS, Rossing I, Dirksen H. Pep treatment or physical exercise - effects on secretions expectorated and indices of central and peripheral airway function. A controlled study. in 10th International Cystic Fibrosis Congress. 1988. Sydney.
12. Salh W, Bilton D, Dodd M, Webb AK. Effect of exercise and physiotherapy in aiding sputum expectoration in adults with cystic fibrosis. Thorax 1989; 44(12): 1006-1008.
13. Aquino A, Balestri E, Dall'Ara S, Lami I, Gobbi F, Ambroni M, Miano A. Efficacy of physical exercise playing a video game for mucus clearance in patients with cystic fibrosis. Journal of cystic fibrosis 2006; 5(Suppl 1): S83 A374.
14. Balestri E, Ambroni M, Dall'Ara S. Efficacy of physical exercise for mucus clearance in patients with cystic fibrosis. Pediatric Pulmonology 2004; 38(Suppl 27): 316 A368.
15. Cerny FJ. Relative effects of bronchial drainage and exercise for in-hospital care of patients with cystic fibrosis. Physical Therapy 1989; 69(8): 633-639.
16. Lannefors L Wollmer P. Mucus clearance with three chest physiotherapy regimes in cystic fibrosis: A comparison between postural drainage, pep and physical exercise. European Respiratory Journal 1992; 5(6): 748-753.
17. Reix P, Aubert F, Werck-Gallois MC, Toutain A, Mazzocchi C, Moreux N, Bellon G, Rabilloud M, Kassai B. Exercise with incorporated expiratory manoeuvres was as effective as breathing techniques for airway clearance in children with cystic fibrosis: A randomised crossover trial. Journal of Physiotherapy 2012; 58(4): 241-247.

Very well written, complete, and nicely done

Good job, clear review

Mention OPEP as well as PEP?

Great introduction - Regarding reference 4, you could include who has set those research priorities (i.e. ? is it people with CF and clinicians)

ACTs and PEP devices are "the cornerstones" rather than one of the cornerstones

What is the intensity of exercise being used within these trials? Is there a dose-response relationship?

Should activity also be included aswell as exercise?

What is meant by 'trend' for mucus clearance?

Is timing of exercise worth no precede ACT?

Also, do note that ACT will oft conjunction with nebs etc

Would it be useful to include the term 'forced expiratory technique' with something to the effect of 'also referred to as a huff' in brackets when the term is first mentioned

Not sure if it is within the scope - but would it be worth mentioning the use of exercise for ACT in the stable person with CF versus someone who is experiencing an exacerbation of their respiratory disease? Someone may feel that exercise + huff is effective when they are well, but less effective when they are unwell / higher sputum load etc.

Good job

Nice abstract. Also as it says top 10 research priorities, defined by whom ?

Outcome measures

Is it worth mentioning the issues / challenges with outcome measures such as expectorated sputum and mucus clearance as this may impact the position statement considerably?

can we turn the position statement into 2 sentences the first advocating exercise with huff and cough improving mucus clearance. Then a second sentence to state there is no medium to long term evidence for exercise as a replacement for ACT.

Query

Is it worth mentioning the need for expiratory flow bias to clear and exercise not creating this, being one theory as to why Huffs are recommended to be included with exercise? Otherwise looks great to me!

Really nice

May be worth some PPI on this - patients that I have spoken to suggest that 'dry huffing' is really unpleasant e.g. when they exercise they do a self-check to see if there are secretions there and then do FET/huff but if dry they just carry on exercising Hope that makes sense - just think that getting patient input to this section would be good

Lovely summary and well written. Would explain what the term Huff means as it's not readily accessible term for all.

the abbreviation AC could be used for airway clearance after the first mention perhaps

o_w_tomlinson + 6 • 1m

5.2 Modulators

CLINICAL CONSIDERATIONS - MODULATORS

Cystic fibrosis transmembrane regulator (CFTR) modulator therapies target the basic biochemical defect (defective CFTR protein) in cystic fibrosis. Treatments work by correcting CFTR (e.g. Lumacaftor, Tezacaftor, Elexacaftor, VX-121) or potentiating the effects of CFTR by allowing the CFTR-dependent chloride channel at the cell surface (e.g. Ivacaftor) to remain open for longer and enhance chloride transport.

Ivacaftor (Kalydeco®) is a CFTR potentiator that increases 'open probability' for the CFTR-dependent chloride channel at the cell surface [1]. Ivacaftor has been reported to increase FEV_1 by > 10% in people with CF with at least one copy of the G551D mutation [2, 3], with benefit also being reported for non-G551D gating mutations [4]. Case reports suggest promising effects of Ivacaftor on exercise capacity [5, 6], whilst a small cross-over study demonstrated improved exercise duration and quality of life with Ivacaftor versus placebo [7]. More recently, Kaftrio® has been shown to improve FEV_1 by 10-14% in clinical trials, with concomitant improvements in weight and quality of life [8, 9], however to date there is no published evidence showing the effects on exercise capacity or physical activity levels. Trials of new modulators e.g. VX-121 in combination with Tezacaftor and Ivacaftor (Vertex Pharmaceuticals) are also in progress.

The exercising subject with CF on Kaftrio®may thus be physiologically advantaged with improvements in ventilatory capacity, skeletal muscle mass and mitochondrial density – making them potentially more 'trainable', however no studies have yet been undertaken in this area.

There is a unique opportunity to understand the 'before' and 'after' of exercise physiology in the modulator era. Careful consideration needs to be given to the best measurements for such studies (CPET, physical activity monitoring, tests of muscle function), as well as avoiding pitfalls encountered by others e.g. ensuring standardisation of equipment, correcting measures for lean body mass to eliminate weight gain as a confounder, taking into account the effects of baseline fitness [10]. Finally, an attempt should be made to ensure that similar, individualised exercise counselling is given to participants in such studies – standardising their trainability.

As an increasing number of pwCF transition onto CF modulator therapy, we suggest that a standardised, combined approach to exercise testing (multimodal assessments of both aerobic fitness and skeletal muscle function) may represent an important next step in advancing our understanding of how the pathophysiology of CF and new treatments *truly* impact physical function. Furthermore, such an approach will help us to move closer to the goal of individualised exercise prescription and personalised medicine, more effectively meeting the needs and wishes of pwCF.

Position Statement: The clinical efficacy of CFTR modulator therapy on the fitness and physical activity behaviours of people with CF is currently unclear, but globally standardised exercise testing will help us understand any potential effects as well as allowing the best possible exercise counselling to be offered.

REFERENCES
1. Van Goor, F., et al., *Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770.* Proceedings of the National Academy of Sciences, 2009. **106**(44): p. 18825-18830.
2. Ramsey, B.W., et al., *A CFTR potentiator in patients with cystic fibrosis and the G551D mutation.* New England Journal of Medicine, 2011. **365**(18): p. 1663-1672.
3. Davies, J.C., et al., *Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation.* American journal of respiratory and critical care medicine, 2013. **187**(11): p. 1219-1225.
4. De Boeck, K., et al., *Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation.* Journal of Cystic Fibrosis, 2014. **13**(6): p. 674-680.
5. Saynor, Z.L., et al., *The effect of ivacaftor in adolescents with cystic fibrosis (G551D mutation): an exercise physiology perspective.* Pediatric Physical Therapy, 2014. **26**(4): p. 454-461.
6. Quon, B.S., et al., *Physiological mechanisms of dyspnea relief following ivacaftor in cystic fibrosis: a case report.* Respiratory physiology & neurobiology, 2015. **205**: p. 105-108.
7. Edgeworth, D., et al., *Improvement in exercise duration, lung function and well-being in G551D-cystic fibrosis patients: a double-blind, placebo-controlled, randomized, cross-over study with ivacaftor treatment.* Clinical Science, 2017. **131**(15): p. 2037-2045.
8. Middleton, P.G., et al., *Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele.* New England Journal of Medicine, 2019. **381**(19): p. 1809-1819.
9. Heijerman, H.G., et al., *Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial.* The Lancet, 2019. **394**(10212): p. 1940-1948.
10. Wilson, J., et al., *VO2max as an exercise tolerance endpoint in people with cystic fibrosis: Lessons from a lumacaftor/ivacaftor trial.* Journal of Cystic Fibrosis, 2020.

0 0

Cite the manufacturer after the first mention of their products, on line 2.

1 0

The author has outlined how CFTR modulators can improve lung function very well. However, could the author also include a passage about how CFTR modulators can effect other well known mediators of exercise capacity (e.g. skeletal muscle mass, inflammation, dysglycaemia).

5 0

Can the author support these statements - that CFTR modulators can enhance mitochondrial density - with scientific literature. Whilst I support the hypothesis, it's not currently clear in the text how the author has generated this hypothesis.

2 0

The summary seems to lose focus from paragraph 3, or discuss the types of exercise tests that are required giv information. Additionally, in light of the new 'future direc more appropriate there.

For the general interest of the CF community, this state the current evidence that has investigated the effects c capacity (e.g. lung, cardiovascular, metabolic and inflan discuss the physiological rationale for why such improv could result in improved aerobic fitness/physical activity studies in which exercise has been used as an outcome

2 0

Suggest

As there is a lack of evidence, maybe to describe the effect of Kalydeco in exercise capacity in the cases reports.

1 0

There is no supporting evidence for the statements in paragraph 3. However likely, we cannot make this statement without evidence, which I suppose is the crux of the problem. May need a re word.

1 0 1

exercise counselling bit in the statement seems misplaced. Why not focus on stating the likely improvements in physical function of people with CF, their feeling of better health and the opportunities this will open up for enhanced physical activity

0 0

It could be nice to add to this section that modulators will increase life expectancy and potentially reduce treatment burden which may have an impact on the role of PA and exercise in CF management in future.

4 0

I think the way this is written it makes it seem like there are only two or three studies looking at exercise outcomes on modulator therapies. Admittedly there are few but I think it might be wo mentioning all of them very briefly. I see the work Wilson (2020) was mentioned in the final paragrap but I think it is worth discussing their 2020 pilot R in paragraph 2.

Wark (2019) ran an observational trial that might b worth mentioning. However, they only looked at 6MWT.

0 0

Could it be worth mentioning the benefits of using exercise as an adjuvant therapy to modulators?

0 0

o_w_tomlinson ✦ 10 ✵ 1m

5.3 Risks of Activity & Exercise

RISKS OF PHYSICAL ACTIVITY AND EXERCISE IN CF

Physical activity is defined as any bodily movement produced by skeletal muscles which requires energy expenditure [1]. Physical activity and exercise have been shown to improve health and fitness in both healthy and clinical populations, and are integral to standard cystic fibrosis (CF) care [2]–[4]. CF disease specific benefits are enhanced airway clearance [5], improved ion channel function potentially leading to better mucus hydration and enhanced mucus clearance [6], [7], a slower rate of decline of lung function [8], improved glycemic control [9], increased bone mineral density [10] [11], enhanced quality of life [12], [13] and a positive association of higher fitness level with survival [14].

Evidence-based guidelines for physical activity and exercise prescription for people with CF have been published [2], [3] and risks for participating in physical activity and exercise have been described [15]. Reports of serious adverse reactions (SARs) related to exercise in patients with CF have ranged from no SARs [9], [16], [17], [18], to studies reporting an incidence of SARs of less than 1% [4], [19]. More commonly, mild adverse reactions have been documented during exercise and include muscle fatigue, cough, wheezing, shortness of breath and headache [20]–[22] and muscle stiffness [23].

The risk of developing exercise induced hypoxemia (EIH), where SpO_2 falls below 90%, is higher in patients with CF than in than healthy individuals [4], [24] and the risk of EIH is correlated to disease severity [25], [26], [27]. As disease progresses, people with CF may require supplementary oxygen to ensure saturation levels are maintained > 90% during exercise [22], [24].

The risk of hypoglycaemia exists for patients with CF-related diabetes mellitus (CFRD) [22]. For these patients, care should be taken to develop a pre, during and post-exercise nutrition plan to ensure that blood sugar levels remain within appropriate levels.

It is well recognized that people with CF are at an increased risk of sodium deficiency due to increased sweat production and altered sweat composition [28], which may increase the risk of dehydration and hyponatraemia, particularly during prolonged exercise and/or in warm or hot conditions. Sports drinks may be an appropriate recommendation for people with CF for before, during and after exercise, especially in hot conditions or for longer durations.

There are specific sports that present specific risks for patients with CF. Exercise at high altitude may increase the risk of desaturation and right heart failure [29], [30] and scuba diving may increase risk of pneumothorax [29]. Finally, contact sports should be avoided in patients with advanced lung disease, liver disease and those with low bone density [29]. Cross contamination among patients with CF must be considered in any exercise plan.

Conclusions
While the advantages of physical activity and exercise for most patients with CF far outweigh the risks, there are contraindications which need to be highlighted for patients and their families, especially once disease severity is increased. Appropriate measures can be taken to mitigate risks for patients with CF that can ensure that exercise and physical activity remain accessible.

Position statement: Physical activity and exercise are strongly recommended for patients with cystic fibrosis. While the incidence of adverse events is rare, guidance should be provided to all patients around hydration, nutrition, exercise intensity and exercise duration.

REFERENCES

[1] "WHO 2020 Physical activity." 2020. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/physical-activity

[2] T. Radtke, S. J. Nevitt, H. Hebestreit, and S. Kriemler, "Physical exercise training for cystic fibrosis," *Cochrane Database Syst. Rev.*, Nov. 2017, doi: 10.1002/14651858.CD002768.pub4.

[3] A. Swisher, "Exercise and habitual physical activity for people with cystic fibrosis: Expert consensus. Evidence-based guide for advising patients," *Cardiopulm Phys Ther J*, vol. 26, no. 4, pp. 85–98, 2015.

[4] S. Rand and S. A. Prasad, "Exercise as part of a cystic fibrosis therapeutic routine," *Expert Rev. Respir. Med.*, vol. 6, no. 3, pp. 341–352, Jun. 2012, doi: 10.1586/ers.12.19.

[5] M. McIlwaine, "Chest physical therapy, breathing techniques and exercise in children with CF," *Paediatr. Respir. Rev.*, vol. 8, no. 1, pp. 8–16, Mar. 2007, doi: 10.1016/j.prrv.2007.02.013.

[6] A. Hebestreit, U. Kersting, B. Basler, R. Jeschke, and H. Hebestreit, "Exercise Inhibits Epithelial Sodium Channels in Patients with Cystic Fibrosis," *Am. J. Respir. Crit. Care Med.*, vol. 164, no. 3, pp. 443–446, Aug. 2001, doi: 10.1164/ajrccm.164.3.2007168.

[7] T. J. Dwyer, R. Zainuldin, E. Daviskas, P. T. P. Bye, and J. A. Alison, "Effects of treadmill exercise versus Flutter® on respiratory flow and sputum properties in adults with cystic fibrosis: a randomised, controlled, cross-over trial," *BMC Pulm. Med.*, vol. 17, no. 1, p. 14, Dec. 2017, doi: 10.1186/s12890-016-0360-8.

[8] J. E. Schneiderman *et al.*, "Longitudinal relationship between physical activity and lung health in patients with cystic fibrosis," *Eur. Respir. J.*, vol. 43, no. 3, pp. 817–823, Mar. 2014, doi: 10.1183/09031936.00055513.

[9] N. Beaudoin, G. F. Bouvet, A. Coriati, R. Rabasa-Lhoret, and Y. Berthiaume, "Combined Exercise Training Improves Glycemic Control in Adult with Cystic Fibrosis," *Med. Sci. Sports Exerc.*, vol. 49, no. 2, pp. 231–237, Feb. 2017, doi: 10.1249/MSS.0000000000001104.

[10] H. M. Buntain, "Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study," *Thorax*, vol. 59, no. 2, pp. 149–155, Feb. 2004, doi: 10.1136/thorax.2003.006726.

[11] K. Hind, J. G. Truscott, and S. P. Conway, "Exercise during childhood and adolescence: A prophylaxis against cystic fibrosis-related low bone mineral density?," *J. Cyst. Fibros.*, vol. 7, no. 4, pp. 270–276, Jul. 2008, doi: 10.1016/j.jcf.2008.02.001.

[12] P. H. C. Klijn, A. Oudshoorn, C. K. van der Ent, J. van der Net, J. L. Kimpen, and P. J. M. Helders, "Effects of Anaerobic Training in Children With Cystic Fibrosis," *Chest*, vol. 125, no. 4, pp. 1299–1305, Apr. 2004, doi: 10.1378/chest.125.4.1299.

[13] D. Urquhart *et al.*, "Effects of a supervised, outpatient exercise and physiotherapy programme in children with cystic fibrosis: Supervised, O/P Exercise and Physiotherapy in CF-R1," *Pediatr. Pulmonol.*, vol. 47, no. 12, pp. 1235–1241, Dec. 2012, doi: 10.1002/ppul.22587.

[14] P. A. Nixon, D. M. Orenstein, S. F. Kelsey, and C. F. Doershuk, "The Prognostic Value of Exercise Testing in Patients with Cystic Fibrosis," *N. Engl. J. Med.*, vol. 327, no. 25, pp. 1785–1788, Dec. 1992, doi: 10.1056/NEJM199212173272504.

[15] Cystic Fibrosis Trust, "Standards of Care and Good Clinical Practice for the Physiotherapy Management of Cystic Fibrosis (2020) Fourth edition - November 2020, Consensus Document." 2020. [Online]. Available: https://bit.ly/3gfT9zN

[16] S. Kriemler *et al.*, "Effect of supervised training on FEV1 in cystic fibrosis: A randomised controlled trial," *J. Cyst. Fibros.*, vol. 12, no. 6, pp. 714–720, Dec. 2013, doi: 10.1016/j.jcf.2013.03.003.

[17] E. S. Sosa *et al.*, "Intrahospital Weight and Aerobic Training in Children with Cystic Fibrosis: A Randomized Controlled Trial," *Med. Sci. Sports Exerc.*, vol. 44, no. 1, pp. 2–11, Jan. 2012, doi: 10.1249/MSS.0b013e318228c302.

[18] E. Santana-Sosa *et al.*, "Benefits of combining inspiratory muscle with 'whole muscle' training in children with cystic fibrosis: a randomised controlled trial," *Br. J. Sports Med.*, vol. 48, no. 20, pp. 1513–1517, Oct. 2014, doi: 10.1136/bjsports-2012-091892.

[19] K. Ruf, B. Winkler, A. Hebestreit, W. Gruber, and H. Hebestreit, "Risks associated with exercise testing and sports participation in cystic fibrosis," *J. Cyst. Fibros.*, vol. 9, no. 5, pp. 339–345, Sep. 2010, doi: 10.1016/j.jcf.2010.05.006.

[20] A. M. Layton *et al.*, "Telerehabilitation Using Fitness Application in Patients with Severe Cystic Fibrosis Awaiting Lung Transplant: A Pilot Study," *Int. J. Telemed. Appl.*, vol. 2021, pp. 1–7, Feb. 2021, doi: 10.1155/2021/6641853.

[21] S. Denford, S. van Beurden, P. O'Halloran, and C. A. Williams, "Barriers and facilitators to physical activity among children, adolescents, and young adults with cystic fibrosis: a systematic review and thematic synthesis of qualitative research," *BMJ Open*, vol. 10, no. 2, p. e035261, Feb. 2020, doi: 10.1136/bmjopen-2019-035261.

[22] C. Burtin and H. Hebestreit, "Rehabilitation in Patients with Chronic Respiratory Disease Other than Chronic Obstructive Pulmonary Disease: Exercise and Physical Activity Interventions in Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis," *Respiration*, vol. 89, no. 3, pp. 181–189, 2015, doi: 10.1159/000375170.

[23] T. del Corral, M. À. Cebrià i Iranzo, I. López-de-Uralde-Villanueva, R. Martínez-Alejos, I. Blanco, and J. Vilaró, "Effectiveness of a Home-Based Active Video Game Programme in Young Cystic Fibrosis Patients," *Respiration*, vol. 95, no. 2, pp. 87–97, 2018, doi: 10.1159/000481264.

[24] J. R. Yankaskas, B. C. Marshall, B. Sufian, R. H. Simon, and D. Rodman, "Cystic Fibrosis Adult Care," *Chest*, vol. 125, no. 1, pp. 1S–39S, Jan. 2004, doi: 10.1378/chest.125.1_suppl.1S.

[25] D. T. Ryujin, S. C. Mannebach, W. M. Samuelson, and B. C. Marshall, "Oxygen saturation in adult cystic fibrosis patients during exercise at high altitude," *Pediatr. Pulmonol.*, vol. 32, no. 6, pp. 437–441, Dec. 2001, doi: 10.1002/ppul.1155.

[26] K. G. Henke and D. M. Orenstein, "Oxygen Saturation during Exercise in Cystic Fibrosis $^{1-3}$," *Am. Rev. Respir. Dis.*, vol. 129, no. 5, pp. 708–711, May 1984, doi: 10.1164/arrd.1984.129.5.708.

[27] K. Ruf and H. Hebestreit, "Exercise-induced hypoxemia and cardiac arrhythmia in cystic fibrosis," *J. Cyst. Fibros.*, vol. 8, no. 2, pp. 83–90, Mar. 2009, doi: 10.1016/j.jcf.2008.09.008.

[28] D. M. Orenstein, K. G. Henke, D. L. Costill, C. F. Doershuk, P. J. Lemon, and R. C. Stern, "Exercise and Heat Stress in Cystic Fibrosis Patients," *Pediatr. Res.*, vol. 17, no. 4, pp. 267–269, Apr. 1983, doi: 10.1203/00006450-198304000-00007.

[29] A. K. Webb and M. E. Dodd, "Exercise and sport in cystic fibrosis: benefits and risks," *Br. J. Sports Med.*, vol. 33, no. 2, pp. 77–78, Apr. 1999.

[30] M. E. Speechly-Dick, S. J. Rimmer, and M. E. Hodson, "Exacerbations of cystic fibrosis after holidays at high altitude — a cautionary tale," *Respir. Med.*, vol. 86, no. 1, pp. 55–56, Jan. 1992, doi: 10.1016/S0954-6111(06)80150-2.

Acknowledgements: Thanks to Evyatar Frank and Kristina Kaganovich (MFSc students) for helping with the literature review.

0 0 0

Thank you for this. Did you consider including influence of severity of CF.

0 0 0

The section about the benefits of CF in first para could be shortened as dealt with elsewhere

0 0 0

EIH

Can you add more detail here - what is the increased risk, and what is the direction of the association with severity?

What is meant by exercise - is this a test to exhaustion, moderate intensity etc?

Does exercise training reduce risk of EIH?

0 0 0

This definition of PA is used in an earlier section, it could be removed here to free up some space. Likewise the benefits are discussed elsewhere.

6 0 2

< and individualized monitoring of BSLs would be important

1 0 0

There is also some reference to hypo/hyperglycaemia in the 2.5 'other health' section - could make references and message match up?

1 0 0

Would it be possible to comment on haemoptysis?

1 0 1

I think it would be very important to include haemoptysis and pneumothorax in this section

https://www.atsjournals.org/doi/10.1164/rccm.201002-0157OC?url_ver=Z39.88-2003&rfr_id=priid:crossref.org&rfr_dat=cr_pub0pubmed

0 0 0

Are portacaths worth mentioning here too?

0 0 0

---

can take out the forst part of the position statement "Physical activity and exercise are strongly recommended.." and save some words

1 0 0

---

do we need to add into definition of PA [here or elsewhere] "....., whihc requires energy expenditure above the resting state."

0 0 0

---

do you think you need some contextual descriptor in the statement like environmental conditions, nature of competition or recreation and not just the four factors named here

0 0 0

Is first paragraph likely to be covered elsewhere in the document - at risk of repetition

0 0 0

Last line of second paragraph- some of these "mild adverse reactions" were surely desirable during exercise???

0 0 0

I like the positional statement.

1 0 0

Conclusion

I don't think there is a need for a conclusion? I think this is essentially a position statement so maybe these could just be linked and removed the conclusion heading

0 0 0

o_w_tomlinson + 6 • 1m

5.4 Nutrition & Hydration

NUTRITION AND HYDRATION CONSIDERATIONS

Maintaining an active lifestyle in Cystic Fibrosis is crucial for all patients [1] for sustaining a high quality of life and achieve the best prognosis [2]. Since CF patients are susceptible to electrolyte dysregulation and dehydration, a series of concerns should be addressed to accomplish the best exercise results.

Nutrition in Cystic Fibrosis also plays a vital role in the health of patients. High energy, high fat intake diet along with pancreatic replacement therapy (PERT) -if pancreatic inefficiency is present- remains the cornerstone of adequate CF care [3]. As CF individuals have been found to present less energy cost of daily activities (ECA) [4] and also tend to show decreased exercise capacity if undernourished [5], a nutritional program oriented in providing the energy required is essential. In this direction, all CF patients should be educated about their nutritional status and caloric needs to achieve maximal adherence [6]. A high-calorie, high-fat, well-balanced meal two to three hours before rigorous activity should be encouraged, along with a small carbohydrate snack about sixty minutes before exercise. At least two hours after physical activity, a full meal rich in carbohydrates should be acquired to replenish energy balance, while at all times, proper adherence to PERT should always be kept in mind [7]. Every exercise/diet plan should be discussed with the physician and dietician to meet the CF individual's BMI targets, caloric goals, and diet preferences.

Individuals with CF-related diabetes (CFRD) should also be encouraged to adopt a daily physical activity program to improve their exercise capacity and lung function[8, 9]. It is advised that all CFRD individuals should obtain blood glucose measurements before and after exercise to avoid post-exercise hypoglycaemia [10, 11].

Avoidance of electrolyte dysregulation during exercise and maintaining proper hydration poses a challenge for CF individuals. All patients should commence exercise fully hydrated. If physical activity is of low intensity and lasts less than 30 minutes, adequate water intake would be enough for replacing the fluid loss. However, for higher intensity, longer-lasting physical activities (requiring heart rates>120-140bpm for more than 30 minutes), or when performing under excess heat conditions, additional salt supplementation should be encouraged [12]. Isotonic drinks are well absorbed and can be used to replace water [13]. CF individuals should always be cautious for early signs of dehydration during physical activity (sore mouth, dizziness, headaches).

Position statement: Adequate nutrition and hydration are essential for maintaining an active lifestyle for CF individuals. Both energy intake and hydration should be adjusted to meet the elevated caloric and fluid needs of an active, healthy CF person.

REFERENCES

1. Wheatley CM, Wilkins BW, Snyder EM. Exercise is medicine in cystic fibrosis. Exercise and sport sciences reviews. 2011;39(3):155-60.
2. Hebestreit H, Hulzebos EHJ, Schneiderman JE, Karila C, Boas SR, Kriemler S, et al. Cardiopulmonary Exercise Testing Provides Additional Prognostic Information in Cystic Fibrosis. American journal of respiratory and critical care medicine. 2019;199(8):987-95.
3. Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, et al. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clinical nutrition (Edinburgh, Scotland). 2016;35(3):557-77.
4. Johnson MR, Ferkol TW, Shepherd RW. Energy cost of activity and exercise in children and adolescents with cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2006;5(1):53-8.
5. Marcotte JE, Canny GJ, Grisdale R, Desmond K, Corey M, Zinman R, et al. Effects of nutritional status on exercise performance in advanced cystic fibrosis. Chest. 1986;90(3):375-9.
6. Calvo-Lerma J, Hulst JM, Asseiceira I, Claes I, Garriga M, Colombo C, et al. Nutritional status, nutrient intake and use of enzyme supplements in paediatric patients with Cystic Fibrosis; a European multicentre study with reference to current guidelines. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2017;16(4):510-8.
7. Foundation. CF. Nutritional Basics. [Available from: https://www.cff.org/Life-With-CF/Daily-Life/Fitness-and-Nutrition/Nutrition/Getting-Your-Nutrients/Nutritional-Basics.
8. Causer AJ, Shute JK, Cummings MH, Shepherd AI, Wallbanks SR, Allenby MI, et al. The implications of dysglycaemia on aerobic exercise and ventilatory function in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society. 2020;19(3):427-33.
9. Foster K, Huang G, Zhang N, Crisalli J, Chini B, Amin R, et al. Relationship between exercise capacity and glucose tolerance in cystic fibrosis. Pediatric pulmonology. 2018;53(2):154-61.
10. Tran BD, Galassetti P. Exercise in pediatric type 1 diabetes. Pediatric exercise science. 2014;26(4):375-83.
11. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pediatric diabetes. 2018;19 Suppl 27:205-26.
12. Lewis DP, Hoffman MD, Stuempfle KJ, Owen BE, Rogers IR, Verbalis JG, et al. The need for salt: does a relationship exist between cystic fibrosis and exercise-associated hyponatremia? Journal of strength and conditioning research. 2014;28(3):807-13.
13. UK CFDG. Staying hydrated and cystic fibrosis 2019 [Available from: https://www.cysticfibrosis.org.uk/sites/default/files/2020-12/Staying%20hydrated%20and%20cystic%20fibrosis%20July%202019.pdf.

1 0 0

Rewording option: 'Maintaining an active lifestyle is crucial for people with CF in order to optimise quality of life and prognosis'

2 0 0

No need for "In this direction.."

1 0 0

Is it worth emphaising these consequences heightened when exercising? could insert "..dysregualtion and dehydration, and potentially exacerbated when exercising, a series of concerns....."

0 0 0

Can the authors provide explicit recommendations regarding how people with CFRD can safeguard from hypoglycaemic events using nutritional strategies. Or, rescue remedies if exercise-induced hypoglycaemia does occur.

1 0 1

Perhaps beyond the scope of this section but would it be possible to comment on the use of supplements or perhaps provide a citation if this is discussed elsewhere?

1 0 0

Could the points here about hypoglycaemia be linked to other statements about hypos. I think continuous monitoring at 24 hours post activity is also recommended when monitoring the longer term effect of activity on blood sugar regulation.

1 0 0

Not sure the physician is best person to advise/discuss exercise with the pwcf as many would frequently defer to other exercise professionals/ physios. Dietitian definitely is essential but possibly state MDT as a whole as diabetic nurse specialist is extremely helpful in these situations too.

0 0 0

would "...adjusted before, during and after physical activity to meet...." precise the statement better?

0 0 0

I felt reading this, that "here is a topic outside my scope of practice ". Perhaps a comment about the major role of a CF specialist Dietitian to work in conjunction with a physiotherapist or ex specialist in the position statement

2 0 0

PHYSICAL ACTIVITY AND EXERCISE FOR CYSTIC FIBROSIS:

A CONSENSUS STATEMENT

Meeting Document

Wednesday 30th June & Thursday 1st July 2021

Hosted by the Children's Health and Exercise Research Centre,

University of Exeter

CONTENTS

1. CHAIRS WELCOME

It gives me great pleasure to welcome everyone to this consensus meeting and I extend my sincere thanks for all the hard work that has gone into its preparations. The idea for the consensus meeting was initiated about six years ago, as part of a wider research proposal to the UK Cystic Fibrosis Trust. It is therefore fantastic to see it taking shape and what I hope will be a stimulating two days of discussion.

I am very appreciative to the participants who have contributed to the writing of synopses, which have encapsulated the cystic fibrosis literature about physical activity and exercise for people with cystic fibrosis with such expertise. I hope our holistic perspective about the role of physical activity and exercise as a promoter of good health and mental well-being will strongly resonate with the CF community, not just because of these COVID times, but due to the noted functional changes of modulator therapies.

I believe this consensus meeting, and the resulting support for the statements we produce, will provide a unique summary of the role physical activity and exercise can play in the lives of people with CF, their family, and friends. In publishing the executive summary style statements, I hope that it will help to drive continued interest, promote clinical research investigations, and support advocacy in this topic.

Finally, I look forward to seeing many of you, albeit virtually over the coming days,

Best wishes.

Professor Craig A. Williams
June 29th, 2021

2. CONSENSUS MEMBERS

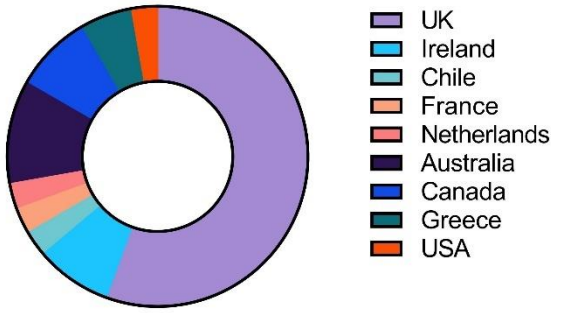
This group is an international and multi-disciplinary panel, consisting of academic and clinical personnel, with a mix of established and early-career professionals.

Group members have been sourced via multiple channels, to reflect the range of academic and professional strengths that exist in this field, and ensure a well-rounded group is obtained. Panel Group members have been identified through their membership of the Youth Active Unlimited Strategic Research Centre, the Association of Chartered Physiotherapists in Cystic Fibrosis, the UK CF & Exercise Technicians Network, and the European Cystic Fibrosis Society Exercise Working Group. We would like to thank the respective Chairs of each group – Lisa Morrison, Dr James Shelley, Dr Thomas Radtke and Dr Don Urquhart – for their assistance in disseminating information about this project.

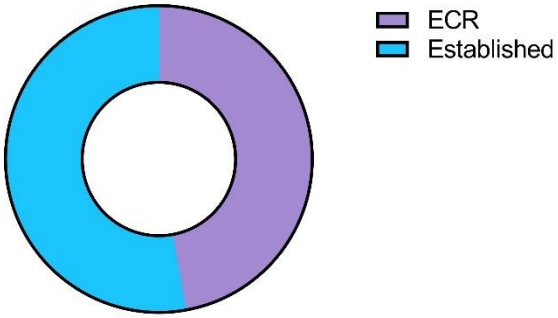
Within the meeting itself, we will also be joined by additional clinical members of the University of Exeter SRC group from the Royal Devon & Exeter NHS Foundation Trust as our primary clinical partners, as well as members of the CF community, including the Cystic Fibrosis Trust; ensuring this document remains of benefit to the wider CF community.

2.1. ***Panel Demographics***

There are 36 people on this panel who have contributed towards the research of topics and synthesis of evidence, with the demographics of this groups laid out below, alongside a full list of contributors.



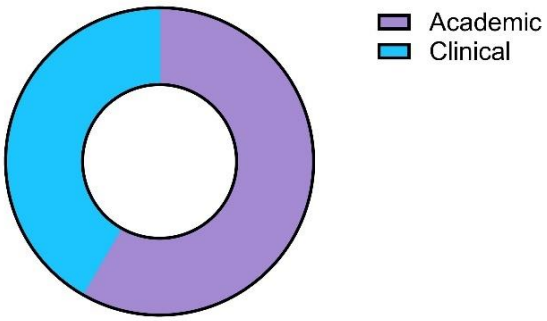
Total=36



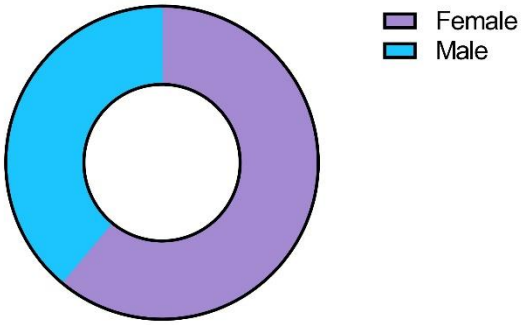
Total=36

443 Years

The combined experience of this consensus group in cystic fibrosis care and research.



Total=36



Total=36

2.2. ***Panel Members***

Name	Position	Institution
Peter Anderson	Clinical Specialist Physiotherapist	Royal Hospital for Children, Glasgow, UNITED KINGDOM
Alan R Barker	Associate Professor of Paediatric Physiology and Health	Children's Health and Exercise Research Centre, Sport and Health Science, University of Exeter, Exeter, UNITED KINGDOM
Zelda Beverley	Specialist CF Physiotherapist	Adult Cystic Fibrosis Unit, Royal Brompton Hospital, London, UNITED KINGDOM
Mayara Silveira Bianchim	Research Fellow	University of Stirling, NMAHP Research Unit, University of Stirling, Stirling, UNITED KINGDOM
Ronan Buckley	Senior Physiotherapist	National Referral Centre for Adult Cystic Fibrosis, St Vincent's University Hospital, Dublin, REPUBLIC OF IRELAND
Brenda M Button	Respiratory Physiotherapy Stream Leader, Department of Respiratory Medicine; Adjunct Clinical Associate Professor	Department of Medicine Nursing and Health Sciences, Monash University, Melbourne, AUSTRALIA Department of Respiratory Medicine, Alfred Health, Melbourne, AUSTRALIA
Jessica Elizabeth Caterini	Medical Student	Translational Medicine, The Hospital for Sick Children, Toronto, CANADA School of Medicine, Queen's University, Kingston, CANADA
Adam John Causer	Research Associate	Department for Health, University of Bath, Bath, UNITED KINGDOM
Narelle Cox	Senior Research Fellow	Allergy, Clinical Immunology and Respiratory Medicine, Monash University, The Alfred Centre, Melbourne, AUSTRALIA Institute for Breathing and Sleep, Monash University, The Alfred Centre, Melbourne, AUSTRALIA
Maire Curran	Senior Physiotherapist and PhD Student	School of Allied Health, University of Limerick, Limerick, REPUBLIC OF IRELAND University Hospital Limerick, Limerick, REPUBLIC OF IRELAND

		Health Research Institute, University of Limerick, Limerick, REPUBLIC OF IRELAND
Sarah Denford	Research Fellow	Health Protection Research Unit in Behavioural Science and Evaluation at the University of Bristol, Bristol, UNITED KINGDOM Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UNITED KINGDOM School of Psychological Science, University of Bristol, Bristol, UNITED KINGDOM
Tiffany J Dwyer	Senior Lecturer, Physiotherapist and Clinical Trials Co-ordinator	Discipline of Physiotherapy, Sydney School of Health Sciences, Faculty of Medicine and Health, University of Sydney, Sydney, AUSTRALIA Department of Respiratory Medicine, Royal Prince Alfred Hospital, Camperdown, AUSTRALIA
Warren Gordon	Technical Instructor	Royal Hospital for Children, Glasgow, UNITED KINGDOM
Mathieu Gruet	Associate Professor	Université de Toulon, Laboratoire IAPS, Toulon, FRANCE
Ryan A Harris	Professor	Georgia Prevention Institute, Department of Medicine, Augusta University, Augusta GA, UNITED STATES OF AMERICA
Elpis Hatziagorou	Associate Professor in Respiratory Paediatrics	Paediatric Pulmonology and CF Unit, 3rd Paediatric Department, Aristotle University of Thessaloniki, Thessaloniki, GREECE
H.J. (Erik) Hulzebos	Assistant Professor	Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, THE NETHERLANDS
Asterios Kampouras	Consultant	Paediatric Pulmonology and CF Unit, 3rd Paediatric Department, Aristotle University of Thessaloniki, Thessaloniki, GREECE Paediatric Department, 424 General Military Hospital, Thessaloniki, GREECE
Kelly A Mackintosh	Professor	Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre, School of Sport and Exercise Sciences, Swansea University, Swansea, UNITED KINGDOM

Melitta A McNarry	Professor	Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre, School of Sport and Exercise Sciences, Swansea University, Swansea, UNITED KINGDOM
Lisa Morrison	Principal Physiotherapist	West of Scotland Adult Cystic Fibrosis Unit, Queen Elizabeth University Hospital, Glasgow, UNITED KINGDOM
Marietta Nunez Camara	Pediatric Pulmonologist; Adjunct Teacher	Hospital Carlos Van Buren, Department of Pediatrics, Division of Pulmonary, Cystic Fibrosis & Home Mechanical Ventilation, Valparaíso, CHILE Universidad de Valparaíso, School of Medicine & Postgraduate, Department of Pediatrics, Viña del Mar, CHILE
Sarah Rand	Lecturer and Research Physiotherapist	Physiotherapy, UCL Great Ormond Street Institute of Child Health, London, UNITED KINGDOM
Clare M Reilly	Senior Physiotherapist	National Referral Centre for Adult Cystic Fibrosis, St Vincent's University Hospital, Dublin, REPUBLIC OF IRELAND
Abbey Sawyer	Postdoctoral Research Fellow	Department of Physiotherapy, University of Melbourne, Parkville, AUSTRALIA Institute for Breathing and Sleep, Austin Hospital, Heidelberg, AUSTRALIA
Zoe Louise Saynor	Senior Lecturer in Physical Activity, Exercise and Health	School of Sport, Health and Exercise Science, Faculty of Science and Health, University of Portsmouth, Portsmouth, UNITED KINGDOM
Jane E Schneiderman	Registered Kinesiologist, Exercise Physiologist, Assistant Professor	Division of Respiratory Medicine, Hospital for Sick Children, Toronto, CANADA Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, CANADA
Grace Spencer	Research Assistant	Department of Psychology University of Bath, Bath, UNITED KINGDOM
James Shelley	Research Officer	Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Centre, School of Sport and Exercise Sciences, Swansea University, Swansea, UNITED KINGDOM

Gemma E Stanford	NIHR/HEE Clinical Doctoral Research Fellow and Specialist Physiotherapist in Adult Cystic Fibrosis	Adult Cystic Fibrosis Unit, Royal Brompton Hospital, London, UNITED KINGDOM National Heart and Lung Institute, Imperial College, London, UNITED KINGDOM
Owen William Tomlinson	Associate Research Fellow	Children's Health and Exercise Research Centre, Sport and Health Science, University of Exeter, Exeter, UNITED KINGDOM Royal Devon and Exeter NHS Foundation Trust Hospital, Exeter, UNITED KINGDOM
Don S Urquhart	Consultant and Honorary Reader in Paediatric Respiratory and Sleep Medicine	Department of Paediatric Respiratory and Sleep Medicine, Royal Hospital for Children and Young People, Edinburgh, UNITED KINGDOM Department of Child Life and Health, University of Edinburgh, Edinburgh, UNITED KINGDOM
Samantha B van Beurden	Research Fellow	College of Medicine and Health, University of Exeter, Exeter, UNITED KINGDOM
Craig A Williams	Professor of Paediatric Physiology and Health	Children's Health and Exercise Research Centre, Sport and Health Science, University of Exeter, Exeter, UNITED KINGDOM Royal Devon and Exeter NHS Foundation Trust Hospital, Exeter, UNITED KINGDOM
Greg D Wells	Senior Associate Scientist	Translational Medicine, The Hospital for Sick Children, Toronto, CANADA
Rachel Young	Physiotherapist	All Wales Adult Cystic Fibrosis Centre, University Hospital Llandough, Llandough, UNITED KINGDOM

3. MEETINGS

These sessions will be conducted via Zoom, and will be recorded to ensure an accurate record of the meeting is kept. We will also keep a copy of the chat log that is generated for each session, again to ensure we have an accurate record of this meeting.

These will only be stored on the Zoom server for as little as possible, before being downloaded and kept on a secure drive at the University of Exeter. These will be kept internally for no more than two years, and not shared with any third party without explicit consent/

Day 1 Zoom Link: [REDATCED]

Day 2 Zoom Link: [REEDACTED]

Please do not share the details of the above Zoom links with anyone else.

4. TIMETABLE

The planned timetable for the two days is outlined below. We have scheduled this to accommodate the time-zone differences for colleagues who are significantly in front of, and behind, European time, whilst retaining a logical topic flow. Please do attend as much as you can, to ensure we have high quality discussion, but we equally do not expect people to be waking up at 4am, or staying with us until midnight.

Wednesday 30th June 2021

Time (BST - London)	Time (EDT – Toronto)	Time (AEST – Sydney)	Topic
0900	0400	1800	Welcome & Introductions
0915	0415	1815	Cardiovascular Health
0945	0445	1845	Fitness & Strength
1015	0515	1915	Other Physical Health Benefits
1045	0545	1945	Mental Health
1115	0615	2015	BREAK
1130	0630	2030	Quality of Life
1200	0700	2100	Nutrition & Hydration
1230	0730	2130	LUNCH
1300	0800	2200	Modulators
1330	0830	2230	Lung Health
1400	0900	2300	Musculoskeletal Health
1430	0930	2330	Risks of activity & exercise
1500	1000	0000	SUMMARY & CLOSE

Thursday 1st July 2021

Time (BST - London)	Time (EDT – Toronto)	Time (AEST – Sydney)	Topic
0900	0400	1800	Welcome & Introductions
0915	0415	1815	Airway Clearance
0945	0445	1845	Optimal Training Modes & Styles
1015	0515	1915	Improving Adherence
1045	0545	1945	Staff/Service Requirements
1115	0615	2015	BREAK
1130	0630	2030	Telehealth
1200	0700	2100	Measurement of exercise
1230	0730	2130	LUNCH
1300	0800	2200	Measurement of physical activity
1330	0830	2230	System oriented outcomes
1400	0900	2300	Patient oriented outcomes
1430	0930	2330	Future Directions
1500	1000	0000	THANK YOU & CLOSE

5. TOPICS AND CONSENSUS STATEMENTS

The topics for this consensus document are listed below. These have been broadly split into five main themes, each focusing on a different component of physical activity an exercise for the management of CF.

These have been decided upon following consultation with the literature, being informed by common themes that exist within current guidelines used by CF professionals (as highlighted in Denford *et al*., ERJ Open Research, 6(3)), as well as research priorities that have been established by patients with CF themselves (Rowbotham *et al*., Thorax, 73(4):388).

Section 1: The Rationale for Activity & Exercise in CF – ***Why are these factors important for people with cystic fibrosis?***

- Patient Oriented Outcomes
- System Oriented Outcomes

Section 2: Health Benefits of Activity & Exercise in CF – ***How does changing these factors benefit patients with cystic fibrosis?***

- Lung Health
- Cardiovascular Health
- Musculoskeletal Health
- Fitness & Strength
- Other Physical Health Benefits
- Mental Health
- Quality of Life

Section 3: Measurement of Activity & Exercise in CF – ***How do we monitor these factors?***

- Measurement of Physical Activity
- Measurement of Exercise

Section 4: Prescription of Activity & Exercise in CF – ***How do we facilitate change and get patients moving (more)?***

- Optimal Training Modes & Styles
- Improving Adherence
- Staff/Service Requirements
- Telehealth

Section 5: Clinical Considerations for Activity & Exercise in CF – *What must we also consider when prescribing activity and exercise for patients with cystic fibrosis?*

- Airway Clearance
- Modulators
- Risks of Activity & Exercise
- Nutrition & Hydration

5.1. Position Statements

Below are the position statements that have been developed by each group following the initial literature review, feedback process, and modifications. This does not represent the final list that will be endorsed and published, but the start-point for discussions amongst the team.

The Rationale for Activity & Exercise in CF

1. Physical activity and fitness have positive associations with increased longevity and reduced morbidity for people with CF.
2. There is no evidence to date to suggest a causal relationship between exercise and hospitalisations. However, engagement in PA and exercise has the potential to positively influence hospitalisations, exacerbations, and antibiotic use. Future intervention and longitudinal studies should consider further exploring the impact of exercise on health system outcomes such as exacerbations, hospitalisations, and antibiotic use.

Health Benefits of Activity & Exercise in CF

3. Exercise and physical activity may slow rate of decline in FEV_1 and FVC in cystic fibrosis, improvements seen may be stronger in those with lower FEV_1 and reduction could be different in adults and children as exercising adults may experience a greater benefit in lung function. The type of exercise performed may not be important, as long as it is performed at a high intensity for the training effect.
4. There is currently insufficient evidence to support physical activity and exercise to improve cardiovascular health in CF. However, this statement should be viewed in light of:
    a. There is a lack of research on this topic and there is currently no evidence for a detrimental effect of physical activity and exercise on cardiovascular health.

b. Given the strong evidence base supporting physical activity and exercise to promote cardiovascular health in the general population, people with CF should be encouraged to adopt international physical activity guidelines.

5. There is some evidence that pwCF have structural and functional muscle alterations contributing to reduced exercise performance, and that resistance training improves muscle strength. The effect of exercise interventions on bone health in pwCF are currently unclear.
6. There is overwhelming evidence that exercise which is of adequate frequency and progressive intensity improves fitness in the Cystic Fibrosis patient population.
7. Improved glycaemic control with low incidence of risks such as hypoglycaemic events may be achieved, by people with CF-related dysglycaemia, by participating in moderate activity or exercise.
8. Exercise interventions may modulate inflammation associated with muscle insulin sensitivity and bacterial infection.
9. A growing body of evidence suggests that physical activity can lead to improvements in mental health and wellbeing among the general population. However, there is currently very little evidence for the impact of physical activity on mental wellbeing among individuals with cystic fibrosis. Studies exploring the issue are generally small, heterogenous and of low quality. Further research is needed before any meaningful conclusions can be made.
10. Health related quality of life (HRQoL) is an important and holistic outcome measure that should be included in exercise and activity intervention research but the clinical efficacy of exercise and activity interventions on the different domains of health-related quality of life (HRQoL) remains unclear.

Measurement of Activity & Exercise in CF

11. Accelerometers provide accurate information regarding the volume and accumulation of physical activity, particularly when CF-specific data processes are utilised, but self-report data is still required to provide contextual information.
12. There are many safe, effective, and informative options for exercise testing in those with CF regardless of age or disease severity. Lab-based tests provide greater insights to the mechanisms of exercise (dys)function, but field-based tests can provide useful information if lab-based tests are not available.

Prescription of Activity & Exercise in CF

13. Structured aerobic exercise training, undertaken at a moderate intensity or higher as part of the ongoing therapeutic routine, is likely to offer greater improvements in exercise capacity and other important health outcomes in most people with CF, compared to lower intensity aerobic exercise or strength training alone, though a well-rounded, comprehensive training program (including aerobic, strength, plyometric, flexibility and other training) is desirable.
14. Adherence to habitual physical exercise across the lifespan in CF is challenging. There are no long term studies which yet identify the most useful strategies for supporting ongoing adherence to exercise training and physical activity participation in people with CF. This is a wide open field urgently requiring research.
15. The provision of exercise within CF care is becoming increasingly important and requires additional staffing and expertise. Efforts should be made to standardise education, training and the roles and responsibilities of healthcare professionals involved in the prescription, supervision, and monitoring of exercise services for people with CF and/or to provide CPD opportunities for CF physiotherapists wishing to develop expertise in exercise provision.
16. Clinical efficacy of exercise training delivered by digital means is currently unclear, but it has been shown to be feasible and acceptable to patients with cystic fibrosis, and clinical teams should be encouraged to consider its use.

Clinical Considerations for Activity & Exercise in CF

17. Exercise with huff or cough improves mucus clearance, however there is no medium or long-term evidence to answer the question if exercise can adequately replace ACTs in people with CF.
18. The clinical efficacy of CFTR modulator therapy on the fitness and physical activity behaviours of people with CF is currently unclear, and warrants further study. Including exercise measurements as standard alongside routinely collected clinical data within CF registries may begin to allow a better understanding of the physiological effects of modulator therapies.
19. Physical activity and exercise are strongly recommended for patients with cystic fibrosis. While the incidence of adverse events is rare, guidance should be provided to all patients around hydration, nutrition, exercise intensity and duration, with respect to the context in which the exercise is performed.

20. Adequate nutrition and hydration are essential for maintaining an active lifestyle for CF individuals. Both energy intake and hydration should be adjusted to meet the elevated caloric and fluid needs of an active, healthy CF person.

Future Directions

21. With the increasing life expectancy in people with CF, it is important to understanding the role of physical activity and exercise to manage potential cardiovascular related co-morbidities. Future work should focus on:
    a. Cross-sectional and prospective studies to quantify the associations between physical activity and cardiovascular health.
    b. Development of randomised controlled trials to examine the effect of exercise training (aerobic, anaerobic and/or mixed) on cardiovascular health.
22. Additional studies are necessary to accurately quantify changes in FFM in response to exercise, with data collection modalities (e.g., magnetic resonance imaging) that can measure localized muscle volume in the specifically trained muscles.
23. Future studies should test the effectiveness of supervised weight bearing exercise interventions and extend the interventions to the growing cohort of older adults with CF as the prevalence of osteoporosis and osteopenia increase with age in CF. As the combination of over-nutrition and improved CFTR function can alter energy balance and will further promote weight gain, future trials enrolling overweight and obese pwCF should also consider modulation in fat mass as a primary endpoint.
24. Research determining whether exercise training can affect oxidative stress is warranted.
25. Research determining the incidence of both hypo- and hyperglycaemia following vigorous intensity exercise is warranted.

6. GUIDE FOR MEETING

Following the production of the above consensus points, we will spend the majority of these two days discussing the literature that has been sourced (as shown in *Summaries of Evidence* below), and the *exact* phrasing of the consensus points above.

As this meeting is being conducted virtually, and each pair will have 30 minutes 'on the floor', we need to adhere to a strict timeline. Therefore, each session will run as shown below:

1. Each pair will present their slides on their topic area, briefly highlighting the importance of this theme for people for CF, noting key papers and the relative strength/weakness of the evidence, and how this literature has informed their present statement. **5 minutes.**
2. Following the presentation, **CAW** will lead a discussion with the whole group to clarify certain points and explore/refine understanding about how the current evidence can be used to inform the consensus, and how this directly affects the wording of yje statements. **20 minutes.**
    a. We will ask people to use the 'Raise Hand' function in Zoom if they would like to have the floor to make a statement/comment. We will keep track f who has their hands raised, and will endeavour to ensure as many people have the chance to speak as possible. Therefore, we will ask that any point/comment does not take more than two minutes in order for us to get through as many people as possible. Preference will always be afforded to the presenting pair in any 30-minute block.
    b. We also encourage use of the 'chat box' function so that people can make additional comments that will give support/dissent to statements, and suggestions for changes to wording should they be required.
3. At the 25 minute mark, **OWT** will give a 5 minute warning.
4. The final part of each section will then be used to *confirm* the final wording of the statement. As this will have been evolving within the past 20 minutes, it is anticipated this will used to formally agree the statement. **5 minutes.**

Following the two-day meeting, all 'final' statements will then be emailed to all attendees as an anonymous survey. This will then allow people the opportunity to vote on the statements, declaring whether they agree, or disagree, with them. If a statement reaches a majority of 'agree' votes, then this will be carried forward into the final consensus document for publication.

	1st Draft Statements (pre-feedback)	2nd Draft Statements (post-feedback)	Final Statements (post-voting)
Rationale for Activity & Exercise in CF	1. Although resistance training can be beneficial compared to no training, aerobic training at least 150 minutes per week is the most effective at improving overall quality of life in CF. 2. Physical activity and fitness have positive associations with increased longevity and reduced morbidly for people with CF. 3. The effect of activity and exercise on health system outcomes in CF requires further investigation. There is no evidence to date to suggest a causal relationship between exercise and hospitalisations. Future intervention and longitudinal studies should consider further exploring the impact of exercise on health system outcomes such as exacerbations, hospitalisations, and antibiotic use.	1. Physical activity and fitness have positive associations with increased longevity and reduced morbidity for people with CF. 2. There is no evidence to date to suggest a causal relationship between exercise and hospitalisations. However, engagement in PA and exercise has the potential to positively influence hospitalisations, exacerbations, and antibiotic use. Future intervention and longitudinal studies should consider further exploring the impact of exercise on health system outcomes such as exacerbations, hospitalisations, and antibiotic use.	1.Physical activity and exercise contribute to increased survival in people with cystic fibrosis and can also improve an individual's sense of overall well-being. 2.Engagement in physical activity and exercise has the potential to positively influence the cost associated with hospitalisations, exacerbations, and antibiotic use.
Health Benefits of Activity & Exercise in CF	4. Exercise can reduce the rate of decline in FEV_1 in cystic fibrosis. 5. There is currently insufficient evidence to support physical activity and exercise to improve markers of cardiovascular health in cystic fibrosis. 6. There is some evidence that pwCF have structural and functional muscle alterations contributing to reduced	3. Exercise and physical activity may slow rate of decline in FEV_1 and FVC in cystic fibrosis, improvements seen may be stronger in those with lower FEV_1 and reduction could be different in adults and children as exercising adults may experience a greater benefit in lung function. The type of exercise performed may not	3.Physical activity and exercise can slow the rate of decline of lung function in people with cystic fibrosis. 4.Physical activity and exercise can improve cardiovascular health in people with cystic fibrosis, however there is limited research on this topic. 5.Resistance training improves limb muscle strength in people with cystic fibrosis.

	exercise performance, and that resistance training improves muscle strength. Additional studies are necessary to accurately quantify changes in FFM in response to exercise, with data collection modalities (e.g. magnetic resonance imaging) that can measure localized muscle volume in the specifically trained muscles. The effect of exercise interventions on bone health in pwCF are currently unclear. Future studies should test the effectiveness of supervised weight bearing exercise interventions and extend the interventions to the growing cohort of older adults with CF as the prevalence of osteoporosis and osteopenia increase with age in CF. As the combination of over-nutrition and improved CFTR function can alter energy balance and will further promote weight gain , future trials enrolling overweight and obese pwCF should also consider modulation in fat mass as a primary endpoint. 7. There is overwhelming evidence that activity and exercise at sufficient intensity and duration improves fitness and strength in the Cystic Fibrosis patient population. 8. Evidence for the benefits of exercise in the management of glycaemic control is scarce, but	be important, as long as it is performed at a high intensity for the training effect. 4. There is currently insufficient evidence to support physical activity and exercise to improve cardiovascular health in CF. However, this statement should be viewed in light of: a. There is a lack of research on this topic and there is currently no evidence for a detrimental effect of physical activity and exercise on cardiovascular health. b. Given the strong evidence base supporting physical activity and exercise to promote cardiovascular health in the general population, people with CF should be encouraged to adopt international physical activity guidelines. 5. There is some evidence that pwCF have structural and functional muscle alterations contributing to reduced exercise performance, and that resistance training improves muscle strength. The effect of exercise interventions on bone health in pwCF are currently unclear. 6. There is overwhelming evidence that exercise which is of adequate frequency and progressive intensity	6. Exercise of adequate frequency and progressive intensity improves fitness in people with cystic fibrosis. 7. Improved glycaemic control with low incidence of risks such as hypoglycaemic events may be achieved, by people with cystic fibrosis-related dysglycaemia, by participating in moderate intensity activity or exercise. 8. Exercise interventions may modulate inflammation associated with muscle insulin sensitivity and bacterial infection. 9. There is currently very little evidence for the impact of physical activity or exercise on mental wellbeing, depression, and anxiety among people with cystic fibrosis; however, studies exploring these issues are generally low quality. 10. Health-related quality of life is an important and holistic outcome measure that should be included in physical activity and exercise intervention research, but the clinical effectiveness of physical activity and exercise interventions on the different domains of health-related quality of life remains unclear.

	indications of improved glycaemic control with low incidence of hypoglycaemic events led to recommendations for moderate activity or exercise for people with CF-related dysglycaemia. 9. Exercise interventions may modulate inflammation associated with muscle insulin sensitivity and bacterial infection. However, future research determining whether exercise training can affect oxidative stress is warranted. 10. There is currently very little evidence to support the impact of physical activity on mental health. However, studies reviewed are generally small, heterogenous and of low quality. Further research is needed before any meaningful conclusions can be made. 11. Health related quality of life (HRQoL) is an important and holistic outcome measure that should be included in exercise and activity intervention research but the clinical efficacy of exercise and activity interventions on the different domains of health related quality of life (HRQoL) remains unclear. 12. Future research should focus on interventions that: a. Investigate the impact when psychosocial interventions are included in parallel.	improves fitness in the Cystic Fibrosis patient population. 7. Improved glycaemic control with low incidence of risks such as hypoglycaemic events may be achieved, by people with CF-related dysglycaemia, by participating in moderate activity or exercise. 8. Exercise interventions may modulate inflammation associated with muscle insulin sensitivity and bacterial infection. 9. A growing body of evidence suggests that physical activity can lead to improvements in mental health and wellbeing among the general population. However, there is currently very little evidence for the impact of physical activity on mental wellbeing among individuals with cystic fibrosis. Studies exploring the issue are generally small, heterogenous and of low quality. Further research is needed before any meaningful conclusions can be made. 10. Health related quality of life (HRQoL) is an important and holistic outcome measure that should be included in exercise and activity intervention research but the clinical efficacy of exercise and activity interventions on the different domains of health-related quality of life (HRQoL) remains unclear.	

	b. Evaluate the dosage and intensity of exercise and activity needed to impact on HRQoL. c. Use consistent and sensitive outcome measures. d. Recruit individuals with a variety of disease severity.		
Measurement of Activity & Exercise in CF	13. Accelerometers can provide more accurate information regarding the volume and accumulation of physical activity when CF-specific data processes are utilised, but self-report data is still required to provide contextual information. 14. There are many safe, effective, and informative options for exercise testing in those with CF regardless of age or disease severity; lab-based tests potentially provide greater insights but the value of field-based tests should not be discounted, especially with regard to the assessment of more subjective outcomes.	11. Accelerometers provide accurate information regarding the volume and accumulation of physical activity, particularly when CF-specific data processes are utilised, but self-report data is still required to provide contextual information. 12. There are many safe, effective, and informative options for exercise testing in those with CF regardless of age or disease severity. Lab-based tests provide greater insights to the mechanisms of exercise (dys)function, but field-based tests can provide useful information if lab-based tests are not available.	11. Accelerometers provide accurate information regarding the volume and accumulation of physical activity, particularly when tailored for use in people with cystic fibrosis, but self-report data is still required to provide contextual, and complementary, information. 12. There are many safe, effective, and informative options for exercise testing in people with cystic fibrosis regardless of age or disease severity. 13. Laboratory based tests provide greater insights to the determinants of exercise capacity, but field-based tests can provide useful information if laboratory based tests are not available. 14. Standardised methods of exercise testing and physical activity assessment should be utilised to enable within- and between-person comparisons, facilitating the individualisation of physical activity promotion and/or exercise prescription.
Prescription of Activity & Exercise in CF	15. Structured aerobic exercise training, undertaken at a moderate intensity or higher as part of the ongoing therapeutic routine, is likely to offer optimal	13. Structured aerobic exercise training, undertaken at a moderate intensity or higher as part of the ongoing therapeutic routine, is likely to offer greater	15. An individualised and comprehensive training program, undertaken at a moderate intensity or higher, as part of

	improvements in exercise capacity and other important health outcomes in most people with CF, compared to lower intensity aerobic exercise or strength training alone, though a well-rounded, comprehensive training program (including aerobic, strength and other training) is desirable. 16. The provision of exercise within CF care is becoming increasingly important and requires additional staffing and expertise, therefore efforts should be made to standardise education, training and the roles and responsibilities of clinical exercise physiologist working in CF and/or to provide CPD opportunities for CF physiotherapists wishing to develop expertise in exercise provision. 17. Clinical efficacy of exercise delivered by digital means is currently unclear, but it has been shown to be feasible and acceptable to patients with cystic fibrosis, and clinical teams should be encouraged to implement its use.	improvements in exercise capacity and other important health outcomes in most people with CF, compared to lower intensity aerobic exercise or strength training alone, though a well-rounded, comprehensive training program (including aerobic, strength, plyometric, flexibility and other training) is desirable. 14. Adherence to habitual physical exercise across the lifespan in CF is challenging. There are no long term studies which yet identify the most useful strategies for supporting ongoing adherence to exercise training and physical activity participation in people with CF. This is a wide open field urgently requiring research. 15. The provision of exercise within CF care is becoming increasingly important and requires additional staffing and expertise. Efforts should be made to standardise education, training and the roles and responsibilities of healthcare professionals involved in the prescription, supervision, and monitoring of exercise services for people with CF and/or to provide CPD opportunities for CF physiotherapists wishing to develop expertise in exercise provision. 16. Clinical efficacy of exercise training delivered by digital means is currently unclear, but it has been shown to be feasible and acceptable to patients with	the ongoing therapeutic routine is recommended in people with cystic fibrosis. 16. Lifelong adherence to habitual physical activity and exercise across the lifespan is important and challenging, due to the many competing and time-consuming activities. 17. The provision of exercise within cystic fibrosis care is becoming increasingly important and requires additional staffing and expertise at the level required to offer annual exercise testing and prescription, including the option of cardiopulmonary exercise testing. Standardisation of the education, training and roles and responsibilities of exercise specialists and other healthcare professionals responsible for the provision of exercise services is required. 18. Exercise training delivered remotely by video calling is feasible and acceptable to people with cystic fibrosis in a small number of pilot studies, and clinical teams could consider its use as a supplement to face-to-face contact.

		cystic fibrosis, and clinical teams should be encouraged to consider its use.	
Clinical Considerations for Activity & Exercise in CF	18. Exercise with huff or cough improves mucus clearance, however there is no medium or long-term evidence to answer the question if exercise can adequately replace ACTs in people with CF. 19. The clinical efficacy of CFTR modulator therapy on the fitness and physical activity behaviours of people with CF is currently unclear, but globally standardised exercise testing will help us understand any potential effects as well as allowing the best possible exercise counselling to be offered. 20. Physical activity and exercise are strongly recommended for patients with cystic fibrosis. While the incidence of adverse events is rare, guidance should be provided to all patients around hydration, nutrition, exercise intensity and exercise duration. 21. Adequate nutrition and hydration are essential for maintaining an active lifestyle for CF individuals. Both energy intake and hydration should be adjusted to meet the elevated caloric and fluid needs of an active, healthy CF person.	17. Exercise with huff or cough improves mucus clearance, however there is no medium or long-term evidence to answer the question if exercise can adequately replace ACTs in people with CF. 18. The clinical efficacy of CFTR modulator therapy on the fitness and physical activity behaviours of people with CF is currently unclear, and warrants further study. Including exercise measurements as standard alongside routinely collected clinical data within CF registries may begin to allow a better understanding of the physiological effects of modulator therapies. 19. Physical activity and exercise are strongly recommended for patients with cystic fibrosis. While the incidence of adverse events is rare, guidance should be provided to all patients around hydration, nutrition, exercise intensity and duration, with respect to the context in which the exercise is performed. 20. Adequate nutrition and hydration are essential for maintaining an active lifestyle for CF individuals. Both energy intake and hydration should be adjusted to meet the elevated caloric and fluid needs of an active, healthy CF person.	19. Exercise with huff or cough improves mucus clearance, however there is no medium- or long-term evidence if exercise can adequately replace airway clearance techniques in people with cystic fibrosis. 20. The clinical efficacy of CFTR modulator therapy on the fitness and physical activity behaviours of people with cystic fibrosis warrants further study. Including exercise testing measurements as standard alongside routinely collected clinical data within cystic fibrosis registries may begin to allow a better understanding of the physiological effects of modulator therapies. 21. Physical activity and exercise are strongly recommended for people with cystic fibrosis. Although the risk is minimal, guidance should be provided to all people with cystic fibrosis around hydration, nutrition, exercise intensity and duration, based on the specific activity. 22. Both energy intake and hydration should be adjusted to meet the elevated caloric and fluid needs of an active person with cystic fibrosis. Every exercise/diet plan should be discussed with the physician and dietician to meet the individual's body mass index targets, caloric goals, and diet preferences.

Future Directions for Activity & Exercise in CF		23. With the increasing life expectancy in people with CF, it is important to understanding the role of physical activity and exercise to manage potential cardiovascular related co-morbidities. Future work should focus on: a. Cross-sectional and prospective studies to quantify the associations between physical activity and cardiovascular health. b. Development of randomised controlled trials to examine the effect of exercise training (aerobic, anaerobic and/or mixed) on cardiovascular health. 24. Additional studies are necessary to accurately quantify changes in FFM in response to exercise, with data collection modalities (e.g., magnetic resonance imaging) that can measure localized muscle volume in the specifically trained muscles. 25. Future studies should test the effectiveness of supervised weight bearing exercise interventions and extend the interventions to the growing cohort of older adults with CF as the prevalence of osteoporosis and osteopenia increase with age in CF. As the combination of over-nutrition and improved CFTR function can alter energy balance and will further promote weight gain, future trials enrolling overweight and obese	23. The prescription of physical activity and exercise should be individualised for people with cystic fibrosis. All aspects of disease management and personal patient preferences should be considered. 24. Clinical trials in cystic fibrosis should include outcomes associated with physical activity and exercise to understand how lifestyle parameters can be affected by pharmaceutical and non-pharmaceutical interventions. 25. Future trials of physical activity and exercise should seek to include outcomes that are currently under-reported, such as cardiovascular health, mental health, endocrine, inflammatory function, and patient reported outcomes, to help further evaluate the effects of physical activity and exercise upon overall health status. 26. Future research should examine: a. Whether exercise can adequately replace airway clearance techniques. b. The interactive effects of CFTR modulators, physical activity, and exercise. c. Whether certain exercise modalities and/or intensities have beneficial effects upon physical and mental health. d. How to improve adherence, including overcoming barriers, identifying enablers, and developing routines,

		pwCF should also consider modulation in fat mass as a primary endpoint. 26. Research determining whether exercise training can affect oxidative stress is warranted. 27. Research determining the incidence of both hypo- and hyperglycaemia following vigorous intensity exercise is warranted.	to physical activity and structured exercise programmes.

ACT: airway clearance therapy; CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; CPD: continuing professional development; FEV_1: forced expiratory volume in one second; FFM: fat free mass; FVC: forced vital capacity; HRQoL: health related quality of life; pwCF: people with cystic fibrosis.

Contribution	CAW	ARB	SD	SBvB	MSB	JEC	NSC	KAM	MAM	SR	JES	GDW	PA	DB	ZB	RB	BB	AJC	MC	TJD	WG	MG	RAH	EH	EHJH	AK	LM	MNC	CMR	AS	ZLS	GS	JS	GES	DSU	RY	OWT
Conceptualisation	■	■	■					■	■																												■
Development of Protocol	■	■	■																																		■
Literature Searching & Synthesis of Evidence	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Production of Initial Statements	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Critical Feedback of Evidence and Statements	■	■	■	■	■	■	■	■	■	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Participation in Consensus Meeting	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Development of Final Statements	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Endorsement of Final Statements	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Manuscript Preparation	■	■																																			■
Critical Evaluation of Manuscript	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Acceptance of Final Document	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
Agree to be Accountable for Final Version	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■