

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The effects of flexi-bar training on muscle strength and physical performance in older people with dynapenia: the protocol of a randomised controlled trial
AUTHORS	WEI, Ning; Wang, Xinxin; CHEN, Ling; Lyu, Mengyu

VERSION 1 – REVIEW

REVIEWER	Shariman Ismail Universiti Teknologi MARA
REVIEW RETURNED	18-Jan-2021

GENERAL COMMENTS	<p>GENERAL COMMENT: The reviewer believes that this study introduces important scientific protocol related to training, exercise and rehabilitation domain. The protocol may contribute to scientific community in terms of investigation related to the effects flexi-bar training program on muscle strength and physical function in the older population with dynapenia. Please refer to the specific comments for opportunity to increase clarity of the protocol.</p> <p>SPECIFIC COMMENTS:</p> <p>INTROUDCTION Page 4 line 56: spelling error- 'recorded' Page 6 line 38: Is there enough evidence that older population with dynapenia would be able to handle vibration training with flexi-bar without any risk/issue? What level of person with dynapenia that is suitable for such intervention?</p> <p>METHOD Page 7 line 39: Who will identify the prospective participants? What is the expected recruitment rate? How long will be the duration of recruitment? Page 8 line 17: spelling error- 'trial' Page 8 line 59: How would the authors justify that 10 sets of 30-seconds used in the protocol is sufficient? Lee et al. (2018) set 20 minutes per day for similar activity for their study. Therefore, if this protocol is more or less driven based on study carried out by Lee et al. (2018), similar approach should be considered if one is expecting to obtain similar outcome. Page 9 line 7: How can authors evaluate the level of effort performed by each participant during all trials using the flexi-bar are at consistent level? Some participant might not be able to sustain same level of intensity when performing the exercise on each trial. In addition, does the individual training effect during the 4 weeks intervention will be neglected? Page 10 line 52: How would authors defined the dominant hand? Will left-handed participants also be considered for this study? Page 11 line12: Does the influence of footwear on balance and</p>
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	<p>stability will be neglected?</p> <p>Page 12 line 12: Previous study with 12-weeks intervention was adopted for sample size and effect size consideration. Referring previous study with similar length of intervention period (weeks) would be more appropriate. In addition, as per suggested by the authors, the planned intervention (5 times per week, for 4 weeks) could be too intense for some participants and drop-out rate could be high. Therefore, higher number of participants could help to prevent lack of data for analysis due to possible high drop-out rate.</p> <p>Page 12 line 25: What are the strategies to promote participants from dropping out?</p> <p>Page 12 line 38: Which participants will be included in the main analysis? Need to provide clear specification of how data management (from data collection to data analysis) will be conducted. Please also describe how missing data will be handled (or a description of why missing data is unlikely).</p> <p>DISCUSSION</p> <p>Page 13 line 51: Study limitations- Will participants with dynapenia be able to consistently performed the exercise without fail or injury/risk? Squatting with 120-degree knee flexion while handling the flexi-bar, 10 trials, 5 times per week might be too much for some. Reflecting the comments in the Introduction part, is there any risk/issue for person with dynapenia to perform the protocol proposed in this study? Do we have enough evidence to conclude that it is safe to proceed? If we do, where is the evidence?</p>
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REVIEWER	Ashira Hiruntrakul Khon Kaen University
REVIEW RETURNED	23-Jan-2021

GENERAL COMMENTS	<ol style="list-style-type: none"> 1. please addition data about albumin and hemoglobin on dynapenia 2. please more clearly the method for sample size calculation 3. please report about precaution of the test for elderly participants
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REVIEWER	Daniel da Cunha Leme State University of Campinas, Faculty of Medical Sciences
REVIEW RETURNED	20-Mar-2021

GENERAL COMMENTS	<p>Dear Editors,</p> <p>I am very grateful for the opportunity to review this study, which is unique in describing a simple and affordable treatment such as Flexi-bar training for older persons with dynapenia. However, despite this positive aspect, this work has some gaps, which in my view should be clarified and considered during the decision to accept it.</p> <p>1) Dynapenia is a prevalent condition in the elderly and more and more researchers seek to understand the process of reducing muscle strength with ageing in different populations, inserted in the context of the assistance of greater complexity, as well as in health care of less complex, yet researchers are also concerned with how to treat the elderly with dynapenia. It is noteworthy that dynapenia has multiple related factors, therefore the treatment is interdisciplinary, that is, it encompasses nutritional, medicinal and physical rehabilitation aspects, and although the present study is aimed at physical rehabilitation, the authors did not mention the multifactorial characteristic of dynapenia (biological factors involved</p>
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in the genesis of dynapenia) and the relevance of interdisciplinary treatment for this health condition. Thus, the introduction briefly mentions dynapenia and describes excessively as the exclusivity of the study, only the use of Flexi-bar training.

2) Still in the introduction, the authors cited the following sentence, as part of the justification for the present study: "... Flexi-bar is one type of vibration training. It consists of a bar and two weighty rubbers at each end of the bar. Its frequency is 5 Hz. [13] Compared to conventional training, it is portable and feasible for physical training in the older population, especially those with dynapenia. Some previous studies have found long-term Flexi-bar had positive effects on muscle mass in young people [14]..."

I can believe that Flexi-bar training is a "portable" and "viable" alternative for physical training in the general population, but what makes me think it would be a "viable" alternative for elderly people with dynapenia? The authors do not cite references for this. If it really is "viable" for elderly people with dynapenia, present at least studies that show the benefit of Flexi-bar training on the muscular strength of elderly people aged 65 and over with the loss of muscle strength, rather than loss of muscle mass, quoted at the end of the paragraph in question, as mass and strength are completely different muscle properties.

3) Still in the introduction, to justify the gain in muscle strength through the Flexi-bar, the authors cite the study by Meliva (2010), who used only 9 healthy male participants with an average age of 20 years, that is, in the elderly this result can be completely different knowing that the age factor is strongly related to the loss of muscle strength. Thus, would flex-bar training for 4 weeks in dynapenic elderly be sufficient?

4) In the introduction, the authors present the study by Lee et al (2018), which showed better results in TUG and 10MWT in elderly people with stroke. This finding is very relevant and justifies the use of Flexi-bar in the elderly, but in the study by Lee et al (2018), the elderly had a stroke, that is, a highly disabling disease. Thus, any improvement, even if minimal, is a satisfactory gain for these patients, different from what is being proposed. In the case of elderly people with just loss of muscle strength or dynapenia, they may not be in an advanced degree of disability, and yet the loss of muscle strength due to dynapenia is not as focal as in stroke that affects a hemibody, but overall. Dynapenic patients require resistance exercises for upper and lower limbs, with isometric and isotonic contractions, within a pre-established physical rehabilitation program according to the literature. So, what makes me think that the Flexi-bar can be a better alternative to conventional exercises using only dumbbells, shin guards, elastic, seated to standing? These exercises and devices (dumbbells, shin guards, elastic, seated to standing) being extremely accessible.

5)The authors cited insufficient muscle load as a limitation for some patients. This negative point would make the study unfeasible, so there must be a thorough assessment for each elderly patient to measure the degree of muscle strength that he supports and how much he can carry out load during exercise. In fact, minimal loads for an elderly person who can support a greater muscle load would be unnecessary from the point of view of muscle strength gain. Thus, the conventional exercises mentioned in the previous

	<p>question, seem to be more appropriate in the scope of the choice of individual muscle load, even according to the different phases of dynapenia.</p> <p>In addition, the authors cited the proposed training routine of 5 times a week for 4 weeks as a limitation, which may lead to some patients dropping out. Is this a limitation to be considered not only because of the withdrawal but in methodological terms, as it would only be effective 4 weeks of training 5 times a week, in gaining muscle strength in elderly people with dynapenia? Wouldn't it be better to have a longer interval of up to 8 weeks or more and a spacing between sessions, for example, 3 times a week? Indeed, this proposed protocol may not be efficient both in adherence to treatment and in the results of improving muscle strength. I suggest that the authors think about this.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Shariman Ismail, Universiti Teknologi MARA

SPECIFIC COMMENTS:

INTROUDCTION

1. Page 4 line 56: spelling error 'recorded'

Answer: We have revised that in the text.

2. Page 6 line 38: Is there enough evidence that older population with dynapenia would be able to handle vibration training with flexi- bar without any risk/issue? What level of person with dynapenia that is suitable for such intervention?

Answer: Thank you for posing this question. To our knowledge, there were only a few articles that focused on the older people with dynapenia. No study had examined the safety of flexi-bar for this particular population. Only one study trained the old people with chronic stroke by using flexi-bar and reported no adverse event (Lee et al., 2018). Compared with stroke patients, the older people with dynapenia may not be in an advanced degree of disability. Therefore, we consider the flexi-bar is safe for our participants. In our study, all participants would active the bar with their individual intensities. Thus, it can be used for the participants at different levels of dyanpenia. It would be safer than the training with unified frequency.

METHOD

3. Page 7 line 39: Who will identify the prospective participants? What is the expected recruitment rate? How long will be the duration of recruitment?

Answer: The main investigator (NW) will screen the participants. In consideration of 20% dropout rate, we will recruit 114 participants. At this stage, especially after COVID-19, I'm afraid we cannot estimate the recruitment rate and the duration of recruitment.

4. Page 8 line 17: spelling error 'trial'

Answer: We have revised it in the text.

5. Page 8 line 59: How would the authors justify that 10 sets of 30seconds used in the protocol is sufficient? Lee et al. (2018) set 20 minutes per day for similar activity for their study. Therefore, if this protocol is more or less driven based on study carried out by Lee et al. (2018), similar approach should be considered if one is expecting to obtain similar outcome.

Answer: Thank you for raising this question. In the study of Lee et al. (2018), they just mentioned the training lasted 20 minutes. They did not give more details, eg: the rest time between each sets, duration of each sets. It is obvious that participants cannot active flexi-bar for 20

minutes without rest. There was one study conducting flexi-bar training for 4 motions. Each motion contained 10 sets * 30 second per set (Chung et al., 2018). However, the participants in their study were middle-age people with low back pain, who are much stronger than our participants. So we choose only one motion with 10 sets * 30 second per set at this stage. More studies are needed to investigate the optimal training duration of flexi-bar.

6. Page 9 line 7: How can authors evaluate the level of effort performed by each participant during all trials using the flexi-bar are at consistent level? Some participant might not be able to sustain same level of intensity when performing the exercise on each trial. In addition, does the individual training effect during the 4 weeks intervention will be neglected?

Answer: Thank you for your questions. During the training, the physical therapist will ask the participants to try their best to active flexi-bar. If participants do not try their best, the flexi-bar will stop vibrating. In this case, the therapist will remind the participants to active the flexi-bar more intensively. Considering the participants in our study might be at different levels of health condition, it is better and safe to train them with individual effort. Also, we will ask our participants do not change their lifestyle during training and follow-up periods. This information was added to the Method section.

7. Page 10 line 52: How would authors defined the dominant hand? Will left-handed participants also be considered for this study?

Answer: Both right hand and left hand could be dominant hand. The dominant hand means the usually-used hand (eg: The hand holding a knife when cut something). The left-handed participants will also be considered in this study.

8. Page 11 line12: Does the influence of footwear on balance and stability will be neglected?

Answer: We will ask our participants to wear the same shoes in all assessments to limit the influence of footwear.

9. Page 12 line 12: Previous study with 12-weeks intervention was adopted for sample size and effect size consideration. Referring previous study with similar length of intervention period (weeks) would be more appropriate. In addition, as per suggested by the authors, the planned intervention (5 times per week, for 4 weeks) could be too intense for some participants and drop-out rate could be high. Therefore, higher number of participants could help to prevent lack of data for analysis due to possible high drop-out rate.

Answer: Thank you for your suggestion. After discussing with research team members, we consider it should be better to conduct training 3 time/week for 12 weeks. We have submitted the application for the changes to the Human Ethics Review Board of Wuhan Brain Hospital and ISRCTN.

10. Page 12 line 25: What are the strategies to promote participants from dropping out?

Answer: Thank you for raising this question. We added this part to the manuscript. For the ethical and funding considerations, we will tell our participants that the training and the assessments are totally free. Also, we will cover their transportation fee during training and follow-up period.

11. Page 12 line 38: Which participants will be included in the main analysis? Need to provide clear specification of how data management (from data collection to data analysis) will be conducted. Please also describe how missing data will be handled (or a description of why missing data is unlikely).

Answer: The last observation carried forward of an intention-to-treat analysis will be used for data analysis.

DISCUSSION

12. Page 13 line 51: Study limitations- Will participants with dynapenia be able to consistently perform the exercise without fail or injury/risk? Squatting with 120-degree knee flexion while handling the flexi-bar, 10 trials, 5 times per week might be too much for some. Reflecting the comments in the Introduction part, is there any risk/issue for person with dynapenia to perform the

protocol proposed in this study? Do we have enough evidence to conclude that it is safe to proceed? If we do, where is the evidence?

Answer: After discussing with research team members, we consider it should be better to conduct training 3 times/week for 12 weeks. We have submitted the application for the changes to the Human Ethics Review Board of Wuhan Brain Hospital and ISRCTN. Until now, no study had examined the safety of flexi-bar for the older people with dynapenia. Only one study trained the old people with chronic stroke by using flexi-bar and reported no adverse event (Lee et al., 2018). Compared with stroke patients, the older people with dynapenia may not be in an advanced degree of disability. Therefore, we consider the flexi-bar is safe for our participants.

Reviewer: 2

Dr. Ashira Hiruntrakul, Khon Kaen University

Comments to the Author:

1. please addition data about albumin and hemoglobin on dynapenia

Answer: the background of albumin and hemoglobin was added to the introduction section.

2. please more clearly the method for sample size calculation

Answer: More details were added to the sample size calculation part.

3. please report about precaution of the test for elderly participants

Answer: Thank you for your suggestion. The primary assessments in this study were safely used in the older people with sarcopenia (Wei et al., 2017), who have similar condition to the participant in this study.

Reviewer: 3

Dr. Daniel da Cunha Leme, State University of Campinas

Comments to the Author:

1. Dynapenia is a prevalent condition in the elderly and more and more researchers seek to understand the process of reducing muscle strength with ageing in different populations, inserted in the context of the assistance of greater complexity, as well as in health care of less complex, yet researchers are also concerned with how to treat the elderly with dynapenia. It is noteworthy that dynapenia has multiple related factors, therefore the treatment is interdisciplinary, that is, it encompasses nutritional, medicinal and physical rehabilitation aspects, and although the present study is aimed at physical rehabilitation, the authors did not mention the multifactorial characteristic of dynapenia (biological factors involved in the genesis of dynapenia) and the relevance of interdisciplinary treatment for this health condition. Thus, the introduction briefly mentions dynapenia and describes excessively as the exclusivity of the study, only the use of Flexi-bar training.

Answer: Information about the contributors to dynapenia was added to the introduction. Considering the objectives of this study, the introduction would be better to focus on the consequences of dynapenia, not the contributors.

2. Still in the introduction, the authors cited the following sentence, as part of the justification for the present study: "... Flexi-bar is one type of vibration training. It consists of a bar and two weighty rubbers at each end of the bar. Its frequency is 5 Hz. [13] Compared to conventional training, it is portable and feasible for physical training in the older population, especially those with dynapenia. Some previous studies have found long-term Flexi-bar had positive effects on muscle mass in young people [14]..." I can believe that Flexi-bar training is a "portable" and "viable" alternative for physical training in the general population, but what makes me think it would be a "viable" alternative for elderly people with dynapenia? The authors do not cite references for this. If it really is "viable" for elderly people with dynapenia, present at least studies that show the benefit of Flexi-bar training on the muscular strength of elderly people aged 65 and over with the

loss of muscle strength, rather than loss of muscle mass, quoted at the end of the paragraph in question, as mass and strength are completely different muscle properties.

Answer: Since “Dynapenia” is a relatively new term, there are only 12 clinical trials focused on it. At the same time, “Flexi-bar” is also a new device, we can only find 14 articles on it. Thus, there was no study investigating the effect of Flexi-bar training on dynapenia. However, we do find some studies supported that Flexi-bar training is effective on physical performance in the older people with stroke, which is the only study targeted at the older people (Lee et al., 2018).

2. Still in the introduction, to justify the gain in muscle strength through the Flexi-bar, the authors cite the study by Meliva (2010), who used only 9 healthy male participants with an average age of 20 years, that is, in the elderly this result can be completely different knowing that the age factor is strongly related to the loss of muscle strength. Thus, would flex-bar training for 4 weeks in dynapenic elderly be sufficient?

Answer: Thank you for raising this question. After discussing with research team members, we consider it should be better to conduct training 3 time/week for 12 weeks. We have submitted the application for the changes to the Human Ethics Review Board of Wuhan Brain Hospital and ISRCTN.

4. In the introduction, the authors present the study by Lee et al (2018), which showed better results in TUG and 10MWT in elderly people with stroke. This finding is very relevant and justifies the use of Flexi-bar in the elderly, but in the study by Lee et al (2018), the elderly had a stroke, that is, a highly disabling disease. Thus, any improvement, even if minimal, is a satisfactory gain for these patients, different from what is being proposed. In the case of elderly people with just loss of muscle strength or dynapenia, they may not be in an advanced degree of disability, and yet the loss of muscle strength due to dynapenia is not as focal as in stroke that affects a hemibody, but overall. Dynapenic patients require resistance exercises for upper and lower limbs, with isometric and isotonic contractions, within a pre-established physical rehabilitation program according to the literature. So, what makes me think that the Flexi-bar can be a better alternative to conventional exercises using only dumbbells, shin guards, elastic, seated to standing? These exercises and devices (dumbbells, shin guards, elastic, seated to standing) being extremely accessible.

Answer: As you mentioned, conventional exercises might be more accessible than Flexi-bar. However, theoretically, Flexi-bar might be more efficient than conventional exercises with unified the training duration. It is known that Flexi-bar is one kind of vibration device, which might induce the tonic vibration reflex (Burke et al., 1972; Wilcock et al., 2009). As you know, the vibration stimulates muscle spindle discharges, which activate the monosynaptic and polysynaptic reflex arcs through the afferent nerve fibers causing muscle contraction. Considering the health condition, it is better to train the dynapenic people with the efficient device.

The authors cited insufficient muscle load as a limitation for some patients. This negative point would make the study unfeasible, so there must be a thorough assessment for each elderly patient to measure the degree of muscle strength that he supports and how much he can carry out load during exercise. In fact, minimal loads for an elderly person who can support a greater muscle load would be unnecessary from the point of view of muscle strength gain. Thus, the conventional exercises mentioned in the previous question, seem to be more appropriate in the scope of the choice of individual muscle load, even according to the different phases of dynapenia.

Answer: During the training, the physical therapist will ask the participants to try their best to active Flexi-bar. If participants do not try their best, the Flexi-bar will stop vibrating. In this case, the therapist will remind the participants to active the Flexi-bar more intensively. Considering the

participants in our study might be at different levels of health condition, it is better and safe to training them with individual effort. As I mentioned before, Flexi-bar might more efficient than the conventional exercises due to the tonic vibration reflex.

- In addition, the authors cited the proposed training routine of 5 times a week for 4 weeks as a limitation, which may lead to some patients dropping out. Is this a limitation to be considered not only because of the withdrawal but in methodological terms, as it would only be effective 4 weeks of training 5 times a week, in gaining muscle strength in elderly people with dynapenia? Wouldn't it be better to have a longer interval of up to 8 weeks or more and a spacing between sessions, for example, 3 times a week? Indeed, this proposed protocol may not be efficient both in adherence to treatment and in the results of improving muscle strength. I suggest that the authors think about this.

Answer: Thank you for your suggestion. We will change the training protocol to 3 times/week for 12 weeks.

VERSION 2 – REVIEW

REVIEWER	Shariman Ismail Universiti Teknologi MARA
REVIEW RETURNED	28-May-2021

GENERAL COMMENTS	Thank you for making the effort to revise the manuscript. I believe the authors have adequately addressed all the comments from the last review session.
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REVIEWER	Daniel da Cunha Leme State University of Campinas, Faculty of Medical Sciences
REVIEW RETURNED	17-May-2021

GENERAL COMMENTS	<p>The authors answered the questions clearly, especially with respect to changes in frequency and duration of the training, which seems more rationable. However, the justification to use Flexi-bar training with efficiency device on dynapenic older adults is unclear and the literature is insufficient.</p> <p>In the introduction, the authors claim the Flexi-bar like an efficient device. They cited that "...These findings (on the previous studies) indicate that Flexi-bar training might be an effective approach to enhance muscle strength at the submaximal level..." I would be cautious with this claim. I would say that "...These findings suggested that Flexi-bar training may be an effective approach..."</p> <p>I also suggest the authors revised the translation again for a possible publication.</p> <p>To sum up, I recommend a major revision.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Dr. Daniel da Cunha Leme, State University of Campinas

Comments to the Author:

- The authors answered the questions clearly, especially with respect to changes in frequency and duration of the training, which seems more rationable. However, the justification to use Flexibar training with efficiency device on dynapenic older adults is unclear and the literature is insufficient.

In the introduction, the authors claim the Flexibar like an efficient device. They cited that "...These findings (on the previous studies) indicate that Flexibar training might be an effective approach to enhance muscle strength at the submaximal level..." I would be cautious with this claim. I would say that "...These findings suggested that Flexi-bar training may be an effective approach..." I also suggest the authors revised the translation again for a possible publication. To sum up, I recommend a major revision.

Answer: Thank you for your helpful comments. We revised the "indicate" to "suggested". We added one reference mentioned the other contributors to the dynapenia. Also, we added some references for the flexi-bar training to justify the use of flexi-bar.

VERSION 3 – REVIEW

REVIEWER	Daniel da Cunha Leme State University of Campinas, Faculty of Medical Sciences
REVIEW RETURNED	22-Jul-2021
GENERAL COMMENTS	I'm grateful to Editor for the opportunity to review the manuscript. The authors were able to complete the questions and suggestions made to them. In addition, the references were accordance with the hypothesis of the research.