

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness of a randomised trial of physical activity in Alzheimer's disease: A secondary analysis exploring patient and proxy-reported health-related quality of life measures in Denmark
AUTHORS	Sopina, Elizaveta; Sørensen, Jan; Beyer, Nina; Hasselbalch, Steen Gregers; Waldemar, Gunhild

VERSION 1 - REVIEW

REVIEWER	Francesco D'Amico PSSRU - LSE London (United Kingdom)
REVIEW RETURNED	02-Jan-2017

GENERAL COMMENTS	<p>This paper presents the results of a cost-effectiveness analysis of an exercise intervention that is aimed at improving quality of life of persons with dementia. The topic is definitely relevant and I have enjoyed reading the results of this study. Below some comments that I thought may be useful for the authors:</p> <ul style="list-style-type: none">- Although the intervention has been performed in Denmark, it would be useful to report the economic results also in a more international currency (Euro, British Pound or American Dollar), both in the abstract and in the presentation of the results within the paper.- It would be useful to include in the paper some brief discussion of similar studies that looked at the effectiveness and cost-effectiveness of exercise treatment in dementia and AD.- The paper does not present tables describing summary statistics by intervention group of socio-demographic variables, service use and costs. I think those should be included for clarity and to understand better the statistical power of the sample.- It is mentioned in the paper that a significant proportion of the participants didn't survive within a year from the beginning of the trial. What proportion of them did not survive? Was the population (with mild dementia rather medium or severe) particularly frail? If so, was a "moderate-to-high" exercise intervention (as defined in the paper) appropriate for that particular population? Also in this case, a table of descriptive statistics would help to clarify.- It is reported in the paper that the EQ-5D instrument may be unable to capture improvements from this type of intervention. Are there other outcomes that can be explored in alternative, or perhaps could some sensitivity analysis be performed on the individual EQ-5D domains?- The language of the paper presents some typos and minor errors that should be corrected.
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REVIEWER	Nicolas Farina Brighton and Sussex Medical School, UK
REVIEW RETURNED	11-Jan-2017

GENERAL COMMENTS	<p>This is an interesting manuscript that investigates the cost effectiveness of a physical activity intervention in people with AD. Due to the variety of physical activity interventions that have been designed it is an important step to determine whether these interventions are effective in terms of outcomes but also costs. In general, I feel that this manuscript is well written, though there are some additional detail that would assist in improving the manuscript. It was positive to see that respite from care was acknowledged.</p> <p>Major comments:</p> <p>Methods: Briefly state that the study was ethically approved. Also include any trial registration number.</p> <p>Analysis: Please be explicit in the types of statistical analysis techniques that were run. For example, you say that a correlation was used, was this a Pearson's correlation? If so, were assumptions checked.</p> <p>Results in general: There is a lack of transparency in some of the analysis conducted. I felt at times that there was a lack of detail in terms of statistical values and p values (significant and non-significant). Notably:</p> <ul style="list-style-type: none"> • A table with descriptive data (e.g. means, p values) from the EQ-VAS and EQ-5D would be more useful than the figure in Supplementary Figure 2. For between group differences calculating an effect size would be useful. • Replace figure 1 with a table that includes descriptive data. • Results (EQ measurements): Provide more detail about correlation coefficients and p-value in text, as well as p values. <p>Discussion: It would be worth being more explicit that this cost analysis is limited to this specific exercise intervention, and that the intervention chosen may not be optimum in terms of exercise type, frequency or duration. The other issue is that the findings are limited to your study participant characteristics, and that there may be greater benefits in other groups (e.g. milder AD or people who were completely sedentary prior to intervention), please highlight this.</p> <p>Minor issues:</p> <ul style="list-style-type: none"> • Abstract/Methods: Please briefly state in brackets what you defined as being "mild AD" (e.g. MMS>19) • Abstract: Ensure you capitalise the beginning of sentences after the colon. • Page 4, Para 1, Line 3: Remove "illness" after dementia • Page 4, Para 2: Please provide additional citations for this sentence. • Page 4, Para 3, Line 4: "It has been proposed to ask the caregiver of participants with dementia to act as proxy respondents and complete the outcome measurements on behalf of or as supplement to the participant-completed measurement." Please clarify who has proposed this, be explicit on the advantages and note there are also disadvantages to proxy reports. • Page 7, Para 1, Line 2: Please provide the Mean MMSE score with an additional decimal point. Standard deviations for both age and MMSE would be useful.
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	<ul style="list-style-type: none"> • Discussion: Consider including a description about the difference between generic HRQL vs disease-specific HRQL (e.g. QoL-AD, DEMQOL) and the potential sensitivity of outcomes.
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment: Although the intervention has been performed in Denmark, it would be useful to report the economic results also in a more international currency (Euro, British Pound or American Dollar), both in the abstract and in the presentation of the results within the paper.

Response:

The economic findings have been re-expressed in Euros. Figures 3, 4, 5 and 6 have also been updated to Euros.

Comment: It would be useful to include in the paper some brief discussion of similar studies that looked at the effectiveness and cost-effectiveness of exercise treatment in dementia and AD.

Response:

Additional references and statements on similar studies have been added in the background section – page 4, lines 8 – 11.

Comment: The paper does not present tables describing summary statistics by intervention group of socio-demographic variables, service use and costs. I think those should be included for clarity and to understand better the statistical power of the sample.

Response:

A supplementary table containing demographic variables, as well resource use and costs was added.

Comment: It is mentioned in the paper that a significant proportion of the participants didn't survive within a year from the beginning of the trial. What proportion of them did not survive?

Response:

It appeared very difficult to given an exact proportion, as it would require investigation into national registers based on personal-ID numbers and, therefore, ethical approval, which was deemed not feasible. The statement about survival was taken out.

Comment: Was the population (with mild dementia rather medium or severe) particularly frail? If so, was a "moderate-to-high" exercise intervention (as defined in the paper) appropriate for that particular population? Also in this case, a table of descriptive statistics would help to clarify.

Response:

The exercise program was appropriate for the ADEX population based on the low drop-out rate (4% in the IG and 8% in the CG) and the exercise intensity, which was mean 81.3% (SD 9.7%) of maximal heart rate during the 12 weeks of aerobic exercise. Descriptive statistics are available in the clinical results paper and a reference to this has been made in the results section (page 7, lines 8-9). PASE scores indicating baseline activity levels, which were relatively high, have been added to the supplementary table.

Comment: It is reported in the paper that the EQ-5D instrument may be unable to capture improvements from this type of intervention. Are there other outcomes that can be explored in alternative, or perhaps could some sensitivity analysis be performed on the individual EQ-5D domains?

Response:

This point was further elaborated on page 10, lines 24-30 and additional discussion was added in

lines 31-33.

Comment: The language of the paper presents some typos and minor errors that should be corrected.

Response:

The paper was reviewed and minor changes were corrected.

Reviewer: 2

Major comments:

Comment: Methods: Briefly state that the study was ethically approved. Also include any trial registration number.

Response:

A statement on ethical approval and trial registration numbers was added (page 5, lines 8-9).

Comment: Analysis: Please be explicit in the types of statistical analysis techniques that were run. For example, you say that a correlation was used, was this a Pearson's correlation? If so, were assumptions checked.

Response:

Pearson correlations was used, and all variables were tested for normality, using both visual examination of residuals, as well as Shapiro-Wilk test for normality. This was specified on page 6, line 23.

Comment: Results in general: There is a lack of transparency in some of the analysis conducted. I felt at times that there was a lack of detail in terms of statistical values and p values (significant and non-significant). Notably: A table with descriptive data (e.g. means, p values) from the EQ-VAS and EQ-5D would be more useful than the figure in Supplementary Figure 2. For between group differences calculating an effect size would be useful. Replace figure 1 with a table that includes descriptive data.

Response:

A supplementary table was added, containing the differences in patient and caregiver-rated EQ-5D and EQ-VAS from baseline to 16 for both, as well as statistical comparisons between the control and intervention groups.

Comment: Results (EQ measurements): Provide more detail about correlation coefficients and p-value in text, as well as p values.

Response:

Additional detail on correlation coefficients was added on page 6, lines 15-18, and p-values were added to the correlation coefficients in the following paragraph.

Comment: Discussion: It would be worth being more explicit that this cost analysis is limited to this specific exercise intervention, and that the intervention chosen may not be optimum in terms of exercise type, frequency or duration.

Response:

We agree that a different intervention may have yielded different costs, and this was highlighted on page 9, line 44. However, the intensity of the intervention does not appear to be inappropriate – as indicated by the very low dropout rate (4% for the intervention group). The participants had a mean 81.3% (SD 9.7%) of maximal heart rate during the 12 weeks of aerobic exercise which indicates an appropriate level of exercise intensity.

Comment: The other issue is that the findings are limited to your study participant characteristics, and that there may be greater benefits in other groups (e.g. milder AD or people who were completely

sedentary prior to intervention), please highlight this.

Response:

This point was made on page 10, lines 28 -41.

Comment: Minor issues:

- Abstract/Methods: Please briefly state in brackets what you defined as being “mild AD” (e.g. MMS>19)

This was added

- Abstract: Ensure you capitalise the beginning of sentences after the colon. The beginning of each sentence was capitalised

- Page 4, Para 1, Line 3: Remove “illness” after dementia
Removed

- Page 4, Para 2: Please provide additional citations for this sentence. –
Additional references added

- Page 4, Para 3, Line 4: “It has been proposed to ask the caregiver of participants with dementia to act as proxy respondents and complete the outcome measurements on behalf of or as supplement to the participant-completed measurement.” Please clarify who has proposed this, be explicit on the advantages and note there are also disadvantages to proxy reports.

The sentence was changed to: ‘It is possible to avoid this problem by asking the caregiver of participants with dementia to act as proxy respondents and complete the outcome measurements on behalf of or as supplement to the participant-completed measurement’. A reference was added.

- Page 7, Para 1, Line 2: Please provide the Mean MMSE score with an additional decimal point. Standard deviations for both age and MMSE would be useful.

Additional decimal points and standard deviations were provided for both figures.

- Discussion: Consider including a description about the difference between generic HRQL vs disease-specific HRQL (e.g. QoL-AD, DEMQOL) and the potential sensitivity of outcomes.

A brief statement to this effect has been included in the discussion section.

VERSION 2 – REVIEW

REVIEWER	Francesco D'Amico London School of Economics, United Kingdom
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	I am happy with the responses of the authors to my previous review.
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