

Consensus agreement on the interpretation of the primary outcomes by the authors of:

**Is an integrated treatment of vestibular rehabilitation and cognitive behavior therapy efficacious for persistent dizziness? A randomized controlled trial in a community-based population (the LODIP study)**

Lene Kristiansen<sup>1,5</sup>, Birgit Juul-Kristensen<sup>2</sup>, Kjersti Wilhelmsen<sup>1</sup>, Silje Meland<sup>3,4</sup>, Stein Helge Glad Nordahl<sup>5,6</sup>, Birgitte Espehaug<sup>1</sup>, Richard Clendaniel<sup>7</sup>, Anders Hovland<sup>8,9</sup>, and Liv Heide Magnussen<sup>1</sup>

**Affiliations:**

<sup>1</sup> Department of health and functioning, Faculty of Health and Social sciences, Western Norway University of Applied Sciences, Bergen, Norway

<sup>2</sup> Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark.

<sup>3</sup> Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Bergen, Norway

<sup>4</sup> Research Unit for General Practice in Bergen, The Norwegian Research Centre, NORCE

<sup>5</sup> Norwegian National Advisory Unit on Vestibular Disorders, Dept of Otorhinolaryngol & Head Neck Surgery, Haukeland University Hospital, Bergen, Norway

<sup>6</sup> Department of Clinical Medicine, University of Bergen, Bergen, Norway

<sup>7</sup> Doctor of physical Therapy Division, Department of Orthopedics, Duke University of Medicine, Durham, NC, USA

<sup>8</sup> Department of Clinical Psychology, University of Bergen, Bergen, Norway

<sup>9</sup> Solli District Psychiatric Centre (DPS), Nesttun, Norway

## Introduction

This study focuses on a treatment integrating modified Vestibular Rehabilitation (VR) and Cognitive Behaviour Therapy (CBT) with the overall aim to reduce perceived dizziness-related handicap and improve gait velocity. The hypothesis is that participants receiving the integrated VR-CBT programme will show superior reduction in perceived dizziness-related handicap in addition to increased preferred gait velocity, compared to persons completing a home-exercise programme with telephone follow-up. A feasibility study (1) and study protocol (2) have been published. The statistical analysis plan is available on the clinical trials website (3).

## Aim

The aim of this document is to establish consensus agreement on the interpretation of the primary outcomes (Dizziness Handicap Inventory (DHI) and preferred gait velocity), while all authors are still blinded to the intervention and control group identification, as recommended (4).

The overall goal of the randomised controlled trial is to evaluate the efficacy of a group-treatment integrating VR and CBT (TREATMENT group), compared with advice and suggestions for home-exercises with telephone follow-up (CONTROL group) in persons with persistent dizziness.

## Method

Data from 105 participants were included at baseline and randomised into one of two groups (GROUP A and GROUP B). 19 participants (11 in GROUP A, 8 in GROUP B) withdrew or did not respond prior to 6-month testing and two more participants (1 in each group) withdrew before 12-month testing, giving a drop-out rate of 18 % at 6 months and 20 % at 12 months. Not all participants completed all outcomes at 6- and 12-month testing giving a variation of the "n" on the outcomes.

Satisfactory compliance to treatment was defined as 75% attendance to group-sessions and 80% completion of exercise diary, for the TREATMENT group, and at least 1 telephone session with a physiotherapist in the CONTROL group (2).

The efficacy analyses conducted on the primary outcomes were based on the evaluation of the between-group differences in changes in DHI scores and preferred gait velocity at 6- and 12-month follow up. A linear mixed model with repeated measures was applied, where the blinded group allocation (TREATMENT and CONTROL) and time (6 and 12 months) were treated as categorical variables. A p-value of  $\leq 0.05$  was considered as statistically significant.

## Results

Due to recruitment difficulties inclusion lasted 4 years and was then stopped due to lack of funding. The required sample size was reached for preferred gait velocity (required sample size= 68), but not for the DHI (required sample size: 94).

The group allocations were blinded during analyses where Treatment A and B represents either the TREATMENT group or the CONTROL group.

The results of the primary outcomes are:

Table 1. Observed DHI and gait velocity scores at baseline and at 1<sup>st</sup> and 2<sup>nd</sup> follow up.

	Time of test	GROUP A			GROUP B		
		n	M	SD	n	M	SD
DHI	Baseline	53	48.9	17.6	52	48.9	18.9
	6-month	38	29.8	17.3	42	38.0	21.3
	12-month	40	26.4	20.3	44	35.0	21.4
Preferred gait velocity (m/s)	Baseline	53	1.15	0.20	52	1.20	0.19
	6-month	41	1.25	0.22	40	1.25	0.18
	12-month	39	1.24	0.19	39	1.23	0.23

M= mean, SD = standard deviation; DHI= Dizziness Handicap Inventory

Table 2. Between group comparison of change in mean values from baseline to first and second follow up estimated with linear mixed effect models for repeated measures

	Time of test	GROUP A		GROUP B		Treatment effect B vs A		
		MD	95% CI	MD	95% CI	MD	95% CI	P
DHI	6-month	-17.3	-20.9 to -13.7	-10.4	-13.9 to -7.0	6.8	1.7 to 12.0	0.01
	12-month	-21.1	-25.5 to -16.7	-14.7	-18.9 to -10.5	6.5	-0.3 to 13.2	0.06
Preferred gait velocity	6-month	0.09	0.05 to 0.14	0.05	0.00 to 0.09	-0.04	-0.11 to 0.02	0.20
	12-month	0.10	0.04 to 0.15	0.03	-0.02 to 0.09	-0.06	-0.15 to 0.02	0.16

n = number of participants; MD = mean difference; CI = confidence interval; FU = follow up; DHI= Dizziness Handicap Inventory

DHI: There was a statistically significant larger decrease in mean DHI scores in GROUP A compared to GROUP B at 6 month-follow up (p=0.01). This superior effect of GROUP A is maintained at 12-month follow-up but is no longer statistically significant (p=0.06) (Table 2).

Gait velocity: There was no statistically significant difference in change scores between the two groups at 6- (p= 0.20) and 12-month (p= 0.16) testing (Table 2).

## Conclusion

Overall:

The linear mixed effect model showed significantly between-group superior effect of GROUP A in change scores at 6-month follow-up in DHI. The superior effect was maintained at 12-month follow-up; however, this effect was not statistically significant. There was no significant between-group difference in change scores in preferred gait velocity at 6- and 12-month follow up.

The change in DHI showed improvement larger than the reported minimal clinical group difference of 11 points (5) in GROUP A at both follow-ups and in GROUP B only at 12-month follow-up. The participants increased their preferred gait velocity in both groups, but only participant in GROUP A reached a minimal clinical change of 0.1 m/s (6) at 12-month follow-up.



A total of 21 participant withdrew from the study, giving a total drop-out rate of 20%. The loss-to-follow up was slightly higher in GROUP A compared to GROUP B which may have added bias to the results. The compliance to group treatment and home exercises is not yet known.

Main conclusion:

The main conclusion of this randomized controlled trial is that participants in GROUP A improved their perception of dizziness related handicap significantly more than the participants in GROUP B after 6 months. The dizziness related handicap continued to decrease at 12 months in both groups, but the superior effect of Treatment A was no longer significant. This suggests that GROUP A had a larger influence on change in dizziness related handicap in the short-term, compared to GROUP B. Participants in both interventions improved in the long term, however, with no statistically significant group difference.

There was no group difference in change in preferred gait velocity between the two groups. This suggests that neither of the interventions had superior effect on change in preferred gait velocity.

## Discussion

The following topics are suggested as points of discussion

### GROUP A is TREATMENT and GROUP B is CONTROL

Interpretation of the results from the mixed model analyses with GROUP A as the TREATMENT group (completing VR-CBT) and GROUP B as the CONTROL group (completing home-exercises), shows significantly superior effect on DHI scores at 6 months in the TREATMENT group compared to the CONTROL group. Even though the DHI scores were further reduced at 12-month testing, the superior effect was no longer significant.

There was to no significant difference in group change scores for preferred gait velocity at 6- and 12-month follow-up.

1. The TREATMENT group improves more than the CONTROL group on DHI scores at 6-month testing. This may be due to the integrated treatment of VR and CBT. These participants also had regular scheduled sessions which may enhance exercise compliance. In addition, the group treatment gave the participants the opportunity to discuss and learn from each other, and further to reflect on bodily sensations together with a therapist. This may have led to an increased feeling of control over their symptom resulting in improvements larger than the CONTROL group.
2. The lack of a superior effect between the groups in relation to preferred gait velocity is similar to what has been found in other studies (7, 8).
3. CONTROL group: The exercises conducted at home were not supervised. Even though attempts were made to give a thorough explanation in advance, there may be barriers that influence the

completion of the home-exercise program, which in turn may have led to a smaller improvement in dizziness related handicap compared to the TREATMENT group. Examples of this may be incorrect interpretation of the instructions, presence of avoidance behaviour, and lack of energy.

4. The lack of power in DHI: With a sample size of 80 at 6- and 84 at 12-month follow-up the DHI does not have sufficient power (required sample size:  $n=94$ ) to show a significantly larger effect in change score in the TREATMENT group at 12 months. This may increase the risk of a Type 2 error.
5. Missing: Missing responses/tests may be due different reasons, like for instance not responded to a specific questionnaire, not completed a test and drop-outs from follow-up. If the number of missing responses/ tests in the TREATMENT group at 6- and 12-month follow-up are mainly those improving, the results may indicate a smaller effect of the TREATMENT group. If the number of missing responses/ tests in the TREATMENT group at follow-up are mainly those not improving or getting worse, the results may indicate a larger effect of the TREATMENT group
6. Placebo effect: The placebo effect may be larger in the TREATMENT group as the participants are guided through eight sessions with a physiotherapist. This gives the TREATMENT group a larger advantage with more follow-up compared to the CONTROL group, which may have influenced the results positively.
7. Compliance: There is a potential for higher compliance in the TREATMENT group compared to the CONTROL group (still unknown), and this may contribute to the significant superior effect at 6-month follow-up. However, there was no superior effect in change scores at 12-month. The 12-month follow up was carried out long after completion of the VR-CBT, and both groups had been through a period without regular follow-ups. This may have influenced the non-significant superior effect between to two groups at the 12-month follow-up.

#### GROUP A is CONTROL and GROUP B is TREATMENT

Interpretation of the results from the mixed model analyses with GROUP A as the CONTROL group (completing home-exercises) and GROUP B as the TREATMENT group (completing VR-CBT), shows significantly greater reduction in DHI scores at 6 months in the CONTROL group compared to the TREATMENT group. Even though the DHI scores continued to reduce at 12-month testing, the superior effect in the CONTROL group was no longer significant.

There was to no significant difference in group change scores for preferred gait velocity at both 6- and 12-month testing.

1. The participants in the CONTROL group had a significantly larger reduction in DHI at 6-month testing compared to the TREATMENT group. This may imply that one physiotherapy-session with thorough information regarding dizziness rarely being a sign of dangerous disease, advice that avoidance and inactivity may make the symptom persist or get worse, giving encouragement and suggestions for staying active, and suggestions for home-exercises is adequate to reduce perceived dizziness related handicap. The reason for lack of superior effect in the CONTROL group at 12-month testing may be that the participants in the TREATMENT group used longer time to integrate what they learned in the VR-CBT sessions into everyday life. Another

explanation may be that the group treatment with discussions related to symptoms may have reinforced and perpetuated the perceived impact of their symptoms, which again may have led to a smaller reduction in perceived dizziness related handicap in the TREATMENT compared to the CONTROL group.

2. The lack of a superior effect between the groups in relation to preferred gait velocity is similar to what has been found in other studies (7, 8).
3. The CONTROL group followed a less time-consuming exercise program compared to the TREATMENT group which may have influenced the motivation for the exercises positively.
4. The lack of power in DHI: With a sample size of 80 at 6 and 84 at 12-month follow-up the DHI does not have sufficient power (required sample size:  $n=94$ ) to show a significantly larger effect in change score in the CONTROL group compared to the TREATMENT group. This may increase the risk of a Type 2 error.
5. Missing: Missing responses/tests may be due different reasons, like for instance not responded to a specific questionnaire, not completed a test and drop-outs from follow-up. If the number of missing items in the CONTROL group at 6- and 12-month follow-up are mainly those improving the results may indicate a smaller effect of the CONTROL group. If the number of missing items in the CONTROL group at follow-up are mainly those not improving or getting worse the results may indicate a larger effect of the CONTROL group
6. Compliance: There is a potential for higher treatment compliance in the CONTROL group (still unknown), and this may contribute to the significantly superior effect at 6-month follow-up. It may be that the expectation of regular sessions and daily exercises in the TREATMENT was too much for the participants resulting in lower compliance. Whereas the participants in the CONTROL group could take charge of their own life, and plan when and where to exercise without any external pressure. The lack of superior effect at 12-month follow may be that the TREATMENT group had to take charge of their life and start doing exercises on their own instead of in the group-sessions.

### Other perspectives

Both groups improved beyond minimal clinical change in the DHI, at 6-months only in TREATMENT A. It may be that advice and self-management is an effective and cost-efficient short-term treatment strategy for many people with persistent dizziness to reduce dizziness-related handicap, provided that TREATMENT A is the CONTROL group.



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Consensus of co-authors:

The following approved the blinded interpretations of the main outcomes in the LODIP study:

Lene Kristiansen:

13.11.22

X Lene Kristiansen

Lene Kristiansen  
Phd Student

Birgit Juul-Kristensen:

X Birgit Juul-Kristensen

Birgit Juul-Kristensen  
Associate Professor

Kjersti Thulin Wilhelmsen:

X Kjersti Thulin Wilhelmsen

Kjersti Thulin Wilhelmsen  
Emerita

Silje Mæland:

13.11.22

X Silje Mæland

Silje Mæland  
Associate professor

Stein Helge Glad Nordahl:

X

Stein Helge Glad Nordahl  
Professor

Birgitte Espehaug:

X Birgitte Espehaug

Birgitte Espehaug  
Professor

Richard Clendaniel:

X Richard Clendaniel

Richard Clendaniel  
Assistant professor

Anders Hovland:

X Anders Hovland

Anders Hovland  
Associate professor

Liv Heide Magnussen:

X Liv Heide Magnussen

Liv Heide Magnussen  
Professor



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13.11.22

X *Lene Kristiansen*

Lene Kristiansen  
Phd Student

Birgit Juul-Kristensen:

X

Birgit Juul-Kristensen  
Associate Professor

Kjersti Thulin Wilhelmsen:

X

Kjersti Thulin Wilhelmsen  
Emerita

Silje Mæland:

X

Silje Mæland  
Associate professor

Stein Helge Glad Nordahl:

X *Stein Helge Glad Nordahl*

Stein Helge Glad Nordahl  
Professor

Birgitte Espehaug:

X

Birgitte Espehaug  
Professor

Richard Clendaniel:

X

Richard Clendaniel  
Assistant professor

Anders Hovland:

X

Anders Hovland  
Associate professor

Liv Heide Magnussen:

X

Liv Heide Magnussen  
Professor