PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Comparative effects of dual-task training versus combined exercise training in water and on land on patients with multiple sclerosis: A Study protocol of a randomized factorial trial

Authors

nazary soltan ahmad, sahar; Shojaedin, Seyed Sadredin; Tazji, Mehdi Khaleghi

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Rabiei, Pouya**
Affiliation	**Université Laval, Medicine**
Date	**05-Jun-2024**
COI	**Non**

Thank you for providing me the opportunity to review the study protocol aimed at comparing the influence of cognitive and motor task training, and combined exercise training in water and on land for individuals with Multiple Sclerosis (MS). While I appreciate the effort put forth by the authors, I have several concerns, detailed below.

General Comments:

The primary concern revolves around the feasibility of the study. As this is a protocol outlining the main study's design, it should convincingly demonstrate that the study can be realistically conducted. The protocol describes six groups undergoing 12 weeks of supervised interventions, involving 224 participants with MS, and multiple biomechanical outcomes during a walking task. My concerns are as follows:

1. Rationale for Six Intervention Groups:

- All interventions (DDT and combined) alongside the control are proposed to be conducted both on land and in water. The necessity for control groups needs clarification, particularly if the primary comparison is between DDT and combined exercise. Two control groups appear redundant. A streamlined approach with DDT and combined exercise may suffice to meet your aims and test your hypotheses.

- The execution of cognitive training in water and its differentiation from land-based training needs elaboration. How does the aquatic environment impact the prescribed cognitive training tasks like sustained attention and processing speed? Since the study combines cognitive and motor tasks, isolating the effects of land and water on cognitive tasks seems unfeasible.

- For motor tasks, variations between land and water exercises could yield meaningful data. However, the manuscript does not clearly explain how variables like movement speed will be controlled across environments.

- Concerning combined exercise in water, is there use of an ergometer for cycling? The same question applies to the control group in water.

- Overall, if you aim to compare the effect of land and water training you can target one group of interventions (DDT or combined) and test it on water and land. On the other hand, if you want to compare the interventions, you can ignore the environment. Then you can decrease the number of groups to 2 or 3 (by adding a control group). The justification for six groups as per the manuscript remains unclear.

2. Recruitment Feasibility:

- The manuscript claims a large sample size which differs from the number stated in the registration document. Is this a multicenter study? More details are required here.

- With a stated trial start date of April 6, 2024, and a last follow-up date of July 29, 2024, the timeline to recruit 224 participants, conduct pre-test assessments, provide 12 weeks of intervention, and perform post-test assessments seems overly ambitious, especially if recruitment has not yet commenced. If recruitment is already underway, the term 'prospective registration' would be incorrect. A revision of the registration to reflect more realistic timelines or an amendment of the manuscript to omit prospective registration is recommended.

Abstract:

In the introduction, the phrase "including decreased processing speed, reduced attentional demands, impaired balance, and gait dysfunction" could be replaced with "cognitive training to exercise training". Also, rephrase the aim as: "We explore dual-task training including cognitive and motor exercise with combined exercise in water and on land on the cognition, balance, and gait of individuals with MS."

Introduction:

Details not directly related to the study's aims, such as cerebral blood flow, brain changes, or gray matter, should be omitted. Simplify the hypotheses by stating them directly without explanatory parts that discuss unmeasured variables like cerebral blood flow or mechanoreceptor stimulation and so on.

Overall, while the rest of the manuscript is satisfactory, the feasibility concerns necessitate a significant revision of the study's aims or possibly an overhaul of several sections to align with any new objectives.

Reviewer	**2**
Name	**Swink, Laura**
Affiliation	**Eastern Colorado Veterans Administration**
Date	**08-Jul-2024**
COI	**N/A**

Once distinct and important difference between the dual-task training and combined exercise training is the cognitive training. The table outlined cognitive dual-task training tasks that are essential. However, the primary outcomes does not consider dual-tasking. The outcomes do not account for any changes in dual-task effects (consideration of motor and cognitive dual-task changes or trade-offs). Especially given that the SDMT is the primary outcome, that makes the reader wonder how cognition was measured during dual-tasking. The introduction strongly builds a rationale for why the interaction between physical and cognitive abilities is important yet does not consider the interaction. Therefore, the introduction needs a stronger rationale for why dual-task performance was not assessed or considered. Then the hypotheses need a better rationale for why dual-task training was included.

I'm unsure on when clinicialtrials.gov needs to be registered for a protocol, but I believe since you have IRB approval it should be registered now and stated in the paper.

Review for BMJ Open

Overall: Once distinct and important difference between the dual-task training and combined exercise training is the cognitive training. The table outlined cognitive dual-task training tasks that are essential. However, the primary outcomes does not consider dual-tasking. The outcomes do not account for any changes in dual-task effects (consideration of motor and cognitive dual-task changes or trade-offs). Especially given that the SDMT is the primary outcome, that makes the reader wonder how cognition was measured during dual-tasking. The introduction strongly builds a rationale for why the interaction between physical and cognitive abilities is important yet does not consider the interaction. Therefore, the introduction needs a stronger rationale for why dual-task performance was not assessed or considered. Then the hypotheses need a better rationale for why dual-task training was included.

Dates?

Area	Specific statement	Concern
Abstract	Land and water	Even in the abstract there should be some rationale for the land/water comparison.
Introduction	“evaluating dual-task performance”	Dual-task performance is not being evaluated, single task cognition and single-task kinematics are being evaluated.
Aims and Hypothesis	“cognitive impairment”	Would it be better to state processing speed here? Even though processing speed declines are connected to cognitive impairment in PwMS?
Aims and Hypothesis		Based on the hypotheses it sounds like water-based combined exercise training is the intervention hypothesized to have the greater improvements? Why do DTT? Within this paragraph it seems like the environment is of more interest.
Intervention		The interventions are both well detailed
Outcomes		Should state “primary outcome” and “secondary outcomes” in the headings
Statistical Analysis		Would general linear mixed models be preferrable to repeated measures ANOVAs? Maybe consider if you will have missing data with the intent-to-treat analyses.
Ethics and Dissemination		Is this already registered on clinicaltrials.gov? Please include
Discussion	“These tasks replicate the challenges encountered during everyday tasks like…”	This needs to be explored further. The tasks are still very simulated and in an environment that is not the natural environment. Please explore a bit more how this leads to more ecologically valid studies.
Discussion	“effects of cognitive and motor factors”	This statement sounds as if cognitive and motor factors are both being considered but it is separate and not in the context of dual-tasking.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1

General Comments:
The primary concern revolves around the feasibility of the study. As this is a protocol outlining the main study's design, it should convincingly demonstrate that the study can be realistically conducted. The protocol describes six groups undergoing 12 weeks of supervised interventions, involving 224 participants with MS, and multiple biomechanical outcomes during a walking task. My concerns are as follows:

Q1. Rationale for Six Intervention Groups:
- All interventions (DDT and combined) alongside the control are proposed to be conducted both on land and in water. The necessity for control groups needs clarification, particularly if the primary comparison is between DDT and combined exercise. Two control groups appear redundant. A streamlined approach with DDT and combined exercise may suffice to meet your aims and test your hypotheses.

R1: We appreciate your valuable feedback on our protocol for the 2x2x3 factorial randomized study investigating the effects of dual-task training (DTT) and combined exercise training in individuals with multiple sclerosis (PwMS).

Rationale for Six Intervention Groups: The inclusion of two control groups—one on land and one in water—is essential to our study's design for several reasons:

- **Environmental Impact:** Our hypothesis posits that aquatic environments may enhance cognition and motor function more effectively than land environments due to factors like increased cerebral blood flow and mechanoreceptor stimulation. By having control groups in both environments, we can comprehensively assess the independent effects of the training modalities while accounting for environmental influences.
- **Comparative Analysis:** The presence of control groups allows for a clearer comparison between the active intervention groups (DTT and combined training) and a baseline. This enables us to isolate the specific effects of our interventions on cognitive impairment and biomechanical outcomes, strengthening the validity of our results. Without these controls, it would be challenging to draw meaningful conclusions about the efficacy of the training protocols.
- **Testing Interaction Effects:** Our study aims to examine interaction effects between the type of training (DTT vs. combined) and the training environment (land vs. water). This necessitates distinct control groups to ensure that the results are not confounded by environmental factors, thereby providing a more robust analysis of how these variables interact.

We are confident that the structure of our study with six groups will allow for a comprehensive examination of the primary objective—comparing the effects of DTT and combined exercise training on cognitive impairment—and secondary outcomes related to gait kinetics and kinematics.

Additionally, we would like to clarify that the estimated number of participants is indeed 228, as indicated in the protocol, rather than the 224 mentioned in review.

Q2. The execution of cognitive training in water and its differentiation from land-based training needs elaboration. How does the aquatic environment impact the prescribed cognitive training tasks like sustained attention and processing speed? Since the study combines cognitive and motor tasks, isolating the effects of land and water on cognitive tasks seems unfeasible.

R2.

1. **Aquatic Environment and Cognitive Training Tasks:** The impact of the aquatic environment on cognitive training tasks like sustained attention and processing speed, especially within dual-task frameworks, is an area of growing research interest. The hypothesis of this study, supported by existing literature, suggests that immersion in water may enhance cognitive function through several mechanisms, including increased cerebral blood flow, mechanoreceptor stimulation, and parasympathetic activity. These effects have been demonstrated to improve cognitive function which is already included in page 6 line 123- 125.

In terms of execution, cognitive tasks in water may benefit from the environmental changes induced by hydrostatic pressure and buoyancy. Water immersion has been shown to positively influence brain plasticity and cognitive processes. Thus, while the core structure of the cognitive tasks remains the same across land and water, the physiological differences in the aquatic environment may lead to differential cognitive outcomes, which we aim to measure.

2. **Combining Cognitive and Motor Tasks Across Environments:** combining cognitive and motor tasks is essential for understanding the holistic impact of dual-task training. The dual-task nature of the interventions—where cognitive tasks are performed alongside motor tasks—aims to simulate real-world conditions that PwMS often face, where both cognitive and motor challenges occur simultaneously.

To address the potential confounding effects, we have incorporated a robust control design. Participants in each environment (water and land) will be assigned to either a dual-task or combined training group, allowing us to disentangle the interaction effects of environment and task type on cognitive and motor outcomes. The control groups in both environments will provide a baseline, enabling us to compare the effects of training within and across environments. This design ensures that the unique contributions of the aquatic setting to cognitive performance are examined without assuming that water immersion alone is the sole factor influencing cognitive outcomes.

3. **Feasibility of Isolating Cognitive Effects:** While it may seem difficult to isolate cognitive effects from motor influences in dual-task settings, our study does not seek to fully disentangle these factors. Instead, we aim to explore the interaction effects between cognitive and motor tasks within each environment, providing insight into how aquatic and land-based training differentially affect cognition and motor performance. The use of both dual-task and combined exercise groups further allows for

comparisons between the degree of cognitive engagement and the motor component, which should yield valuable insights into their combined impact on PwMS.

Q3 - For motor tasks, variations between land and water exercises could yield meaningful data. However, the manuscript does not clearly explain how variables like movement speed will be controlled across environments.

R3- The study design ensures that movement speed will be regulated through standardized instructions given to all participants, regardless of environment. Specifically, for motor tasks, participants will be instructed to perform the exercises at a self-selected pace that aligns with their natural movement patterns (page 20, line 377). This self-selected pace has been shown to normalize variations in movement speed across different environments, such as land and water, reducing external influences on performance.

Moreover, the use of kinematic and kinetic data collection systems, such as the Vicon MX T40-S cameras and Kistler force plates, will allow for precise measurement of movement parameters, including speed, stride time, and cadence (page 19, line 367-370). These data will be captured in real-time and normalized across participants, ensuring that differences in movement speed between land and water environments can be quantitatively assessed and adjusted if needed.

These strategies will help us to control for movement speed and other motor variables across land and water environments, ensuring the integrity and comparability of the collected data.

Q4- Concerning combined exercise in water, is there use of an ergometer for cycling? The same question applies to the control group in water.

R4- We confirm that an ergometer will indeed be used for cycling in the water, as part of the combined exercise intervention. The same applies to the control group in water.

For further clarification, the inclusion of the cycle ergometer is mentioned on page 12 (lines 245-247), where it is stated that all interventions, including dual-task training, combined exercise training, and control interventions, will be applied in both environments—land and water. Moreover, as detailed on page 15 (line 290) and page 17 (line 307), the use of a cycle ergometer is justified due to the reduced balance and coordination requirements for PwMS, as compared to treadmill walking.

Q5- Overall, if you aim to compare the effect of land and water training you can target one group of interventions (DDT or combined) and test it on water and land. On the other hand, if you want to compare the interventions, you can ignore the environment. Then you can decrease the number of groups to 2 or 3 (by adding a control group). The justification for six groups as per the manuscript remains unclear.

R5. Thank you for your valuable feedback and suggestions. We appreciate the opportunity to clarify and elaborate on the structure of our study design.

Regarding the justification for six groups and the combination of environmental and intervention comparisons:

The primary aim of this study is to not only compare the *type* of intervention (dual-task training [DTT] vs. combined exercise training) but also to evaluate the *environmental effect* (land vs. water) on both cognitive and motor outcomes in people with multiple sclerosis (PwMS). We hypothesize that the aquatic environment could have distinct benefits on cognition and motor functions compared to land due to factors like increased mechanoreceptor stimulation, improved cerebral blood flow, and enhanced parasympathetic activity in water. Similarly, we expect combined exercise training to improve gait kinetics more effectively than DTT, but this could vary depending on the training environment.

To address the suggestion of reducing the groups, we feel it is critical to maintain the current 2x2x3 factorial design to capture both the intervention and environmental effects. Simplifying the groups by focusing solely on the environment or the intervention would limit the ability to fully explore these interaction effects. Specifically, the unique potential benefits of water-based DTT or combined training on cognition and gait would be missed if we only examined one intervention type across environments. Likewise, reducing the focus to intervention type alone would overlook how environmental factors might modulate the efficacy of these interventions.

Justification for six groups:

- We aim to understand whether water amplifies the effects of DTT and combined training differently than on land. Hence, it is essential to test each intervention in both environments.
- Including a control group for both land and water ensures that any observed changes in the experimental groups are attributable to the interventions rather than environmental exposure alone, thereby enhancing the internal validity of the study.

Thus, the six-group design is necessary to:

1. Isolate the *interaction* effects of intervention type (DTT vs. combined training) and environment (land vs. water) on both cognitive and motor outcomes.
2. Compare how the aquatic environment might modulate the efficacy of these interventions differently from land-based exercises.
3. Ensure rigorous control by having both land and water-based control groups, essential to disentangle the effect of simply being in water or on land.

Feasibility of six groups: To address concerns about feasibility, we have accounted for adequate participant numbers using G*Power software, as outlined in the manuscript, ensuring sufficient power to detect significant differences while managing potential dropout rates.

We hope this clarification adequately addresses the concerns, demonstrating the necessity of maintaining six groups to achieve the study's comprehensive objectives.

Comparison with Similar Studies
Our study design is consistent with multi-arm parallel trials utilized in previous research, demonstrating the validity of employing a factorial design to assess combined treatment effects. Notable examples include:

1. **COGEx Trial**(1, 2): This randomized, blinded, sham-controlled trial investigated the effects of cognitive rehabilitation and aerobic exercise on processing speed deficits in people with progressive MS. The design involved multiple groups to compare different combinations of interventions, emphasizing the need to understand interaction effects between therapies. The authors noted(3), “Regulators usually require that a combination therapy is compared to each component separately to demonstrate the combination is better than either alone to accept the risk of multiple drugs when one might suffice. Factorial designs test the effect of two or more therapies with multiple levels that are crossed. These designs require that each intervention can be administered without changing the dose when administered in combination with the other. Factorial designs allow more efficient testing of two interventions, as fewer patients are needed than if the therapies are tested separately, although interactions between therapies can increase sample size. The COGEx trial, for example, is a randomized, blinded, sham-controlled trial that is testing whether the combination of cognitive rehabilitation and exercise interventions is more effective than the individual therapies and control conditions for improving processing speed deficits in people with progressive MS"(3).

2. **REMIND-MS Study**: This study protocol explored cognitive rehabilitation and mindfulness in MS patients, employing a multi-arm design where participants were randomized into various intervention groups, including cognitive rehabilitation, mindfulness-based cognitive therapy, and enhanced treatment as usual. The findings highlighted the importance of assessing multiple interventions simultaneously to capture their combined effects on cognitive outcomes(4, 5).

Our design not only adheres to established methodologies but also seeks to address critical gaps in understanding how environmental factors, specifically land and water settings, influence the efficacy of cognitive and motor interventions in PwMS.

2.Q6 Recruitment Feasibility:
- The manuscript claims a large sample size which differs from the number stated in the registration document. Is this a multicenter study? More details are required here.

R6: 1. **Sample Size Calculation**: The sample size of 190 participants indicated in the UMIN registration was calculated based on the study's design using G*Power software, with a significance level of 0.05 and a power of 90%. This initial calculation considered the number of participants necessary to achieve statistically significant results for the primary outcomes of the study. However, in the manuscript, I included the adjusted total of 228 participants to account for an anticipated dropout rate of approximately 20%. This adjustment was made to ensure sufficient statistical power and the integrity of the trial results, adhering to best practices in clinical research.

2. **Multicenter Study Design**: This is not a multicenter study. All recruitment, data collection, and interventions will be conducted within the Alborz region of Karaj, Iran, specifically through collaboration with the Alborz MS NGO and neurologists within the area. Recruitment efforts will also extend to community-based channels such as social media (e.g., Instagram) and hospital boards within the region. We have addressed your concern by adding more details about the recruitment strategies and screening procedures on page 10, lines 205–208.

3. **Consistency and Integrity of the Study**: While the UMIN registration states 190 participants, the need for a larger sample size in the manuscript reflects our commitment to conducting a robust study. We will adhere to the originally registered sample size in the UMIN documentation and maintain

transparency regarding the inclusion of dropouts in our analysis. Regardless of the final number of participants who complete the trial, we will conduct intention-to-treat analyses for all initially assigned participants, which aligns with the highest standards of clinical trial methodology.

Q7- With a stated trial start date of April 6, 2024, and a last follow-up date of July 29, 2024, the timeline to recruit 224 participants, conduct pre-test assessments, provide 12 weeks of intervention, and perform post-test assessments seems overly ambitious, especially if recruitment has not yet commenced. If recruitment is already underway, the term 'prospective registration' would be incorrect. A revision of the registration to reflect more realistic timelines or an amendment of the manuscript to omit prospective registration is recommended.

R7.

1. **Prospective Registration Clarification**: The manuscript was submitted on March 26, 2024, before recruitment commenced, in compliance with protocol guidelines. This ensures that the study remains under prospective registration, aligned with UMIN Clinical Trials Registry, as we faced technical issues with the Iranian registry.
2. **Recruitment Strategy and Feasibility**: While the study starts on April 6, 2024, our partnership with the Alborz MS NGO, which has an established network of doctors and MS centers, will facilitate efficient recruitment. This collaboration enables us to recruit participants within the designated timeframe.
3. **Participant Numbers and Timeline Justification**: We aim to recruit 228 participants, accounting for a 20% dropout rate. With the support of the Alborz MS NGO, we are confident in meeting our recruitment goals and have organized immediate pre-test assessments to streamline the process.
4. **Timeline and Rigor**: We understand the timeline appears ambitious; however, we believe our structured approach and collaboration will allow us to achieve our goals. If delays occur, we are ready to adapt while maintaining the study's integrity.

Abstract:

Q 8: In the introduction, the phrase "including decreased processing speed, reduced attentional demands, impaired balance, and gait dysfunction" could be replaced with "cognitive training to exercise training". Also, rephrase the aim as: "We explore dual-task training including cognitive and motor exercise with combined exercise in water and on land on the cognition, balance, and gait of individuals with MS."

R8: Page 2, line33-38: done.

Introduction:

Q9: Details not directly related to the study's aims, such as cerebral blood flow, brain changes, or gray matter, should be omitted. Simplify the hypotheses by stating them directly without explanatory parts that discuss unmeasured variables like cerebral blood flow or mechanoreceptor stimulation and so on.

R9: Pages6-7, lines 123-125/162-164: Regarding the comment on simplifying the hypotheses, we recognize the need to streamline the text. However, concepts like cerebral blood flow and mechanoreceptor stimulation are relevant to the study's aims, as they relate directly to cognitive improvements. While we agree to omit excessive explanatory details Therefore, we simplified the text.

Overall, while the rest of the manuscript is satisfactory, the feasibility concerns necessitate a significant revision of the study's aims or possibly an overhaul of several sections to align with any new objectives.

Reviewer: 2
Dr. Laura Swink, Eastern Colorado Veterans Administration
*** Please find additional comments from this reviewer in the attached file ***
Comments to the Author:
Q1: Once distinct and important difference between the dual-task training and combined exercise training is the cognitive training. The table outlined cognitive dual-task training tasks that are essential. However, the primary outcomes does not consider dual-tasking. The outcomes do not account for any changes in dual-task effects (consideration of motor and cognitive dual-task changes or trade-offs). Especially given that the SDMT is the primary outcome, that makes the reader wonder how cognition was measured during dual-tasking. The introduction strongly builds a rationale for why the interaction between physical and cognitive abilities is important yet does not consider the interaction. Therefore, the introduction needs a stronger rationale for why dual-task performance was not assessed or considered. Then the hypotheses need a better rationale for why dual-task training was included.

R1: Our primary objective is to assess the overall impact of cognitive and motor interventions in different environments—water and land—on cognitive impairment in people with multiple sclerosis (PwMS). The primary outcome, the Symbol Digit Modalities Test (SDMT), is a widely recognized measure of cognitive function and processing speed, which provides a clear and reliable indicator of cognitive changes over time. While dual-task training is part of our intervention strategy, it is the overall cognitive benefit, rather than the interaction between motor and cognitive tasks specifically, that we aim to measure.

Additionally, we chose not to focus on dual-task performance in the primary outcomes because of the complexity of isolating cognitive changes in a dual-task context within aquatic environments, where motor demands differ significantly from those on land.

The water environment inherently reduces the load on musculoskeletal systems, potentially masking or altering the trade-offs typically seen in dual-task scenarios. Hence, our focus remains on assessing the general cognitive outcomes rather than narrowing it down to dual-task effects.

I agree that the introduction builds a rationale for the importance of the interaction between physical and cognitive abilities, which may seem inconsistent with the decision not to assess dual-task performance directly. Let me clarify this further.

In our study, we aim to compare the overall cognitive effects of different training environments (water vs. land) and modalities (dual-task training vs. combined training). Although dual-task training (DTT) involves both cognitive and motor challenges, we did not assess dual-task performance itself as a primary outcome because our focus is on the broader cognitive impact, rather than the interaction between tasks. The primary outcome, the SDMT, was chosen because it provides a validated and robust measure of cognitive function that can be reliably compared across all groups.

The rationale for including dual-task training, despite not directly measuring dual-task performance, stems from its established role in enhancing both cognitive and motor functions. We hypothesize that DTT will lead to improvements in cognitive function, which we are assessing using the SDMT, and that these improvements will be comparable or superior to those achieved through combined training. In essence, while dual-task training includes motor-cognitive interactions, our focus is on the overall cognitive gains it produces rather than the specific trade-offs or changes in dual-task performance.

This approach allows us to investigate how cognitive function responds to training across different environments and modalities while keeping the outcomes broadly applicable and meaningful to a wider range of cognitive measures. Additionally, the aquatic environment introduces unique factors—such as reduced motor load and enhanced mechanoreceptor stimulation—that further justify focusing on general cognitive outcomes rather than task-specific performance.

I hope this provides a stronger rationale for the structure of our hypotheses and clarifies the inclusion of dual-task training without direct assessment of dual-task performance.

Q2: I'm unsure on when clinicialtrials.gov needs to be registered for a protocol, but I believe since you have IRB approval it should be registered now and stated in the paper.

R2: I would like to clarify that the study is already registered with the UMIN-CTR (registration number: UMIN000053947), which is an ICMJE-recognized clinical trial registry. The trial was registered prospectively, as per ICMJE requirements, on March 22, 2024, well ahead of the trial start date (April 6, 2024). Additionally, UMIN-CTR complies with WHO's ICTRP standards. Since. recruitment for the study has been completed. we are unable to register it as a prospective study on ClinicalTrials.gov.

Area	Specific statement	Concern	EXPLANATION
Abstract	Land and water	Even in the abstract there should be some rationale for the land/water comparison.	I have added the rationale for the land/water comparison to the abstract on page 2, lines 35-37.
Introduction	"evaluating dual-task performance"	Dual-task performance is not being evaluated, single task	While dual-task performance (DTP) is often used as a direct measure of cognitive-motor

		cognition and single-task kinematics are being evaluated.	interference, our study focuses on the separate but complementary effects of dual-task training (DTT) and combined training on cognitive and motor outcomes under different environmental conditions (land vs. water). This approach aligns with our primary objective: evaluating improvements in cognition and motor function independently through both types of training. By evaluating cognition and motor function independently through single-task assessments, we can better isolate the impact of each intervention and environmental condition (land vs. water).
Aims and Hypothesis	"cognitive impairment"	Would it be better to state processing speed here? Even though processing speed declines are connected to cognitive impairment in PwMS?	Thank you for your valuable feedback. We chose "cognitive impairment" to reflect the broader range of cognitive deficits in PwMS, not just processing speed. The BICAMS tool we use assesses multiple domains, including verbal and visuospatial memory, alongside processing speed. Focusing solely on processing speed could limit the interpretation of our study's findings, which aim to explore both cognitive and motor outcomes comprehensively. To address your point, we clarified the importance of processing speed by adding: :Given that processing speed decline is central to cognitive impairment, it will be a key outcome to assess intervention effectiveness" page 7, lines 157-158
Aims and Hypothesis		Based on the hypotheses it sounds like water-based combined exercise training is the intervention hypothesized to have the greater improvements? Why do DTT? Within this paragraph it seems like the environment is of more interest.	Thank you for your insightful comments. While the hypothesis suggests that water-based combined exercise training may yield greater improvements, the inclusion of dual-task training (DTT) is essential for several reasons. DTT specifically targets cognitive engagement during physical activity, which is critical for addressing cognitive impairments in people with Multiple Sclerosis. By comparing the effects of DTT and combined exercise training across both water and land environments, we can better understand the interactive effects of cognitive load and environmental context on motor function and cognitive outcomes. This dual focus enhances the study's overall rigor and relevance, allowing us to explore how each intervention uniquely contributes to improving both cognitive and motor performance in PwMS.
Intervention		The interventions are both well detailed	
Outcomes		Should state "primary outcome" and "secondary	To enhance the clarity and organization of the manuscript, we have added distinct headings for

		outcomes" in the headings	the "Primary Outcome" and "Secondary Outcomes" sections which are marked in yellow.
Statistical Analysis		Would general linear mixed models be preferrable to repeated measures ANOVAs? Maybe consider if you will have missing data with the intent-to-treat analyses.	Thank you for your insightful suggestion regarding the use of general linear mixed models (GLMM) instead of repeated measures ANOVAs. Given our study's 2×2×3 factorial design, which includes six groups (dual-task training and combined exercise training in both water and land, plus control groups), we have chosen repeated measures ANOVA to evaluate main effects and interactions effectively. However, we acknowledge the advantages of GLMMs, particularly in managing missing data. To address this concern, we will implement intent-to-treat analyses, ensuring all participants are included in the final assessment regardless of adherence.
Ethics and Dissemination		Is this already registered on clinicaltrials.gov? Please include	Thank you for your feedback regarding trial registration. Our study is currently registered with the UMIN Clinical Trials Registry, and recruitment for the study has been completed. we are unable to register it as a prospective study on ClinicalTrials.gov. page8, lines174-182.
Discussion	"These tasks replicate the challenges encountered during everyday tasks like…"	This needs to be explored further. The tasks are still very simulated and in an environment that is not the natural environment. Please explore a bit more how this leads to more ecologically valid studies.	We acknowledge that our training tasks are conducted in controlled environments (land and water) that may not perfectly replicate real-life scenarios. However, the exercises we have designed aim to closely mimic the cognitive and motor challenges faced in daily activities. For example, our training protocols include tasks such as walking while carrying an object (e.g., a cup of water), which directly simulate everyday activities such as walking while multitasking, which is common in tasks like driving, gardening, or shopping. These activities require individuals to navigate their environment while simultaneously managing cognitive loads, such as memory and attention, thereby providing a relevant representation of the complex demands of daily living. By conducting our study in both land and water environments, we aim to assess not only the effectiveness of different training modalities but also their applicability in various contexts that individuals may encounter in real life. This dual-environment approach enhances the study's ecological validity and allows us to evaluate how different settings may influence cognitive-motor performance in functional tasks. We expanded our discussion to further clarify how these training tasks relate to everyday life

			challenges and how they contribute to the ecological validity of our research, ensuring that we address your concerns adequately. Pages 22-23.
Discussion	"effects of cognitive and motor factors"	This statement sounds as if cognitive and motor factors are both being considered but it is separate and not in the context of dual-tasking	To clarify, our study explicitly investigates the interactions between cognitive and motor factors within the framework of dual-task training. In our design, dual-task training will involve simultaneous cognitive and motor challenges, thereby allowing us to assess the integrated effects of these factors on participants' performance in both aquatic and land environments. This dual focus is critical because it reflects real-life scenarios where individuals often engage in cognitive tasks while performing physical activities. By examining how cognitive load affects motor performance in these two distinct settings, our research aims to fill a significant gap in the literature

VERSION 2 - REVIEW

Reviewer	**1**
Name	**Rabiei, Pouya**
Affiliation	**Université Laval, Medicine**
Date	**21-Nov-2024**
COI	

Thank you for your responses.

Wish you the best with your project.

VERSION 2 - AUTHOR RESPONSE

I would like to kindly clarify that gait and balance are indeed included as secondary outcome measures in the UMIN Clinical Trials registry. Specifically, the registry mentions kinetics and kinematics throughout the balance and gait cycle, encompassing spatiotemporal parameters, sagittal plane angles, moments of the hip, knee, and ankle, as well as anteroposterior, mediolateral, and vertical ground reaction forces.

The secondary outcomes listed in the UMIN Clinical Trials Registry include: The California Verbal Learning Test (CVLT) and the Brief Visuospatial Memory Test (BVMTR) in The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).

kinetics and kinematics throughout the balance and gait cycle, encompassing spatiotemporal parameters, sagittal plane angles, and moments of the hip, knee, and ankle, as well as anteroposterior, mediolateral, and vertical ground reaction forces.

Reviewer: 1
Dr. Pouya Rabiei, Université Laval
Comments to the Author:
Thank you for your responses.
Wish you the best with your project.

R: Thank you for your kind wishes and constructive feedback. We appreciate your time and expertise and are grateful for your support throughout this process.

Wishing you all the best in your endeavors.

Outcome(s)

Primary Outcome	The Symbol Digit Modalities Test (SDMT) in The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS).
Secondary Outcome	The California Verbal Learning Test (CVLT) and The Brief Visuospatial Memory Test (BVMTR) in The Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). kinetics and kinematics throughout the balance and gait cycle, encompassing spatiotemporal parameters, sagittal plane angles, and moments of the hip, knee, and ankle, as well as anteroposterior, mediolateral, and vertical ground reaction forces.

fig1. The secondary Outcome in the UMIN Clinical Trials registry