A 12-month Randomised Pilot Trial of the Alzheimer's and Music Therapy Study: A Feasibility Assessment of Music Therapy and Physical Activity in Patients with Mild-to-Moderate Alzheimer's Disease

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A 12-month Randomised Pilot Trial of the Alzheimer's and Music Therapy Study: A Feasibility Assessment of Music Therapy and Physical Activity in Patients with Mild-to-Moderate Alzheimer's Disease

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Abstract

Background: The Alzheimer's and Music Therapy (ALMUTH) study is the first randomised controlled trial (RCT) design with 12 months of active non-pharmacological therapy (NPT) implementing music therapy (MT) and physical activity (PA) for participants with Alzheimer's disease (AD). The aim of the present article is to retrospectively examine the inclusion of mild-to-moderate Alzheimer's Disease patients into the main ALMUTH study protocol and to determine if continued inclusion of AD patients is warranted.

Methods: The randomised pilot trial was conducted as a parallel three-arm RCT, reflecting the experimental design of the ALMUTH study. The trial was conducted in Bergen, Norway and randomisation (1:1:1) was performed by an external researcher. The study was open label and the experimental design features two active NPTs: MT and PA, and a passive control (no intervention, CON) in Norwegian speaking patients with AD who still live at home and could provide informed consent. Sessions were offered one time per week (up to 90 minutes) up to 40 sessions over the period of 12 months. Baseline and follow-up tests included a full neuropsychological test battery and three magnetic resonance imaging (MRI) measurements (structural, functional, and diffusion weighted imaging). Feasibility outcomes were assessed and were determined as feasible if they met the target criteria.

Results: 18 participants with a diagnosis of mild-to-moderate AD were screened, randomised, and tested at baseline and after a 12-month follow-up interval. Participants were divided into three groups: MT (n=6), PA (n=6), and CON (n=6). Results of the study revealed that the ALMUTH protocol in patients with AD is not feasible. Adherence to protocol was poor (50% attended sessions), the presence of 50% attrition rates, 50% retention rates, insufficient and costly recruitment, issues with study fidelity, and many issues raised by staff. Recruitment status is still ongoing and the main study has been expanded to include milder forms of memory impairment. No adverse events were reported by the patients or their caregivers.

Conclusions: The pilot trial was not deemed feasible in patients exclusively with AD. To mitigate this, the ALMUTH study has expanded the recruitment criteria to include participants with milder forms of memory impairment (pre-AD) in addition to expanding the neuropsychological test battery. The ALMUTH study is currently ongoing.

Trial Registration: Norsk Forskningsråd (NFR) funded. Regional Committees for Medical and Health Research Ethics (REC-WEST: reference number 2018/206). ClinicalTrials.gov: NCT03444181 (registered retrospectively 23 February 2018, https://clinicaltrials.gov/ct2/show/NCT03444181).

Keywords: non-pharmacological therapies, music therapy, physical activity, randomised pilot trial, feasibility, Alzheimer's disease, Longitudinal, randomised controlled trial

Key Messages on Feasibility

What uncertainties about feasibility existed prior to this study?

To our knowledge there are currently no other 12-month RCT neuroimaging studies implementing non-pharmacological therapies in mild-to-moderate AD patients, thus it was uncertain how patients would react to the demands of the ALMUTH study protocol. It is also the only study that evaluates neuroscientific methods in order to investigate the effects of NPTs such as MT and PA on brain plasticity and brain ageing in Alzheimer patients. Since there are uncertainties regarding the recruitment, testing, attrition, retention, and adherence of patients to such an intervention, it was imperative to ensure whether the inclusion of AD patients was feasible and whether the continuation of recruitment of AD individuals was warranted in the main study.

What are the key feasibility findings from this study?

Key feasibility findings of the study revealed that the participants had difficulty adhering to the protocol. Due to acceleration of AD symptoms and disease progression, many patients withdrew from the study leading to an attrition rate of 50% (9/18) and retention rates 50% (9/18). Of those who completed a post-assessment 12-months later, adherence to protocol was 50% with many issues raised by staff for further change or upgrade to the main study protocol. These findings prompted the ALMUTH study to expand the recruitment criteria to pre-AD stages.

What are the implications of the feasibility findings on the design of the main study?

Generally regarded as good practice, the publication of feasibility studies, particularly in phase III trials including randomisation, is very instructive for future studies on Alzheimer's Disease. Implications of the randomised pilot trial revealed that the feasibility of conducting such an intensive, weekly intervention over the course of 12-months, including baseline and follow-up neuropsychological, and neuroscientific assessments in Alzheimer patients was not feasible. These findings allowed the ALMUTH study to expand inclusion criteria to include participants with a diagnosis of Mild Cognitive Impairment and participants who have noticed subjective memory changes and met the criteria for Subjective Memory Decline. The impetus for their inclusion is based on research stating that Alzheimer's disease begins decades before the presentation of AD symptoms (1) and that the preventative use of NPTs in earlier or presymptomatic AD stages may ameliorate disease outcomes.

Background

As the most widespread and fatal progressive neurodegenerative disorder among the elderly, the prevalence of Alzheimer's Disease (AD) has been alarmingly accelerating, making up 60-80% of all dementia cases worldwide (2). Currently 55 million worldwide suffer with dementia and is estimated to double every 20 years (3). These numbers are compounded by the fact that no effective treatment options exist for patients with AD (4),(5). As research has progressed, the pathological development of AD has been recognised to exist on a continuum with the disease beginning in a preclinical phase and developing towards prodromal AD (also known as Mild Cognitive Impairment (MCI) due to AD), and finally expressed as a clinical syndrome of AD dementia with increasing severity impairing activities of daily living (ADL) (2).

The defining pathological features characterising AD are a spatiotemporal spread of amyloid beta (Aβ) protein in senile plaques, tau protein neurofibrillary tangles, neurodegeneration, and vascular amyloidopathy (6),(7). Clinical and cognitive deficits of AD include memory loss that disrupts daily life, challenges in executive functioning, planning, problem solving, trouble understanding images and spatial relationships, changes in mood and personality, withdrawal from work and social activities, decreased judgment, and novel problems with words in speech or writing (2).

As the efficacy of drug interventions for AD has not yet proven to be satisfactory (8),(9), NPTs such as physical exercise, music therapy, light therapy, cognitive behavioural therapy, and diet to prevent and relieve symptoms of AD have been implemented (10),(11). Due to their low cost (12) and relatively easy implementation, NPTs should be used as an adjunct to pharmacotherapy and should be started as early as possible (13), specifically in early and presymptomatic AD stages (14). In healthy aging elders as well as patients with mild AD and dementia, NPTs have also been shown to improve neuroplasticity (15),(16). A study by Shigihara and colleagues (16) showcased that NPTs improve cognitive functioning and behavioural disturbances in dementia patients. The increased integration and use of NPTs in conjunction with approved drug therapies can aid in diminishing the percentage of preclinical and prodromal individuals converting to AD.

Music Therapy in AD

Several studies have shown spared musical memory in patients with AD (17),(18) as evidenced by their ability to recognise familiar music (19). Music activates a broad network in the brain, rather than being localised to a specific area (20),(21). Brain areas underlying musical memory are among the last to show brain atrophy in AD (17), and thus the implementation of music in a medical setting has been encouraged (25),(23). Moreover, music has been shown to reduce anxiety in patients with AD (24), im-

prove cognitive performance in tasks related to verbal and episodic memory , enhance the encoding and retrieval of verbal information (25),(26), and improve autobiographical recall (27),(28).

Research using music therapy can contribute to improvements in cognition and neuropsychiatric symptoms of AD (29),(30), and decreasing symptoms related to agitation, depression, anxiety, and overall behavioural symptoms (24),(31)-(37). Another study showcased that music therapy can increase happiness scores, lower stress levels, and improve emotional state in patients with mild AD (33). A functional magnetic resonance imaging (fMRI) study conducted by Satoh and colleagues (29) using singing training led to improvements in neuropsychiatric symptoms as well as neural efficacy of cognitive processing in patients with AD. Research on singing has also shown positive effects on heart rate variability (34) and social bonding (35). In dementia patients, singing has been shown to improve memory, mood, and the relationship to a caregiver (36).

Additional research using music therapy has been shown to improve attention, psychomotor speed, memory, orientation, and executive functions (29),(37),(38). Meta-analyses (39),(40) have indicated that music therapy has positive effects in AD patients, including improvements of cognitive function, global cognition, quality of life, and ameliorating symptoms of long-term depression. However, the relative methodological quality of such studies was low, resulting in weak effect sizes, and a lack of longitudinal studies demonstrating long-term benefits (41),(32). A meta-analysis of 15 studies by Wang, Zhan, and Cai (42) showed that the effects of MT on cognitive function and activities of daily living (ADL) scores were not significant in patients with AD. A systematic review and meta-analysis by Fusar-Poli and colleagues (40) analysed 110 studies on the effect of MT on cognitive functions in patients with dementia and found that although there were beneficial effects on global cognition, RCT studies with larger sample sizes will be needed to elucidate the impact of MT on cognitive functions in patients with dementia. Thus, there is a lack of solid scientific evidence for positive effects of MT on cognitive function or brain degeneration in AD.

Physical Activity/Exercise Therapy in AD

Physical activity has been implicated as a potential NPT that can help reduce the incidence of dementia and AD. As an estimated 54% of risk factors for developing AD may be preventable (43), it was found that the highest attributable risk factor for developing AD was physical inactivity (44). A literature review by Cass (45) reviewed exercise treatments and AD revealing that exercise can improve brain blood flow, increase hippocampal volume and cognitive performance (46) , and improve neurogenesis. A study which analysed the effect of over a year of mild to moderate physical activity was able to prevent further hippocampal volume atrophy (47). A 14 year population-based prospective study in Germans (48) found that self-reported regular physical activity was associated with a reduction of risk of developing MCI and AD including enhancements in their neuropsychological test scores. Other prospective studies also reported that total physical activity was associated with reduced risk of developing AD (49) and significantly lessened rates of cognitive decline (50).

Some RCT studies have shown mixed efficacy of physical activity on cognitive decline , showing positive effects on ADL scores (51),(52) and neuropsychiatric symptoms (53) but no improvements on behavioural, depressive, or nutritional scores (51) or cognitive performance (53). Conversely, A systematic review and meta-analysis of 6 RCTs found that in patients with AD who underwent an exercise program, there were decreased rates of cognitive decline and positives effects on global cognition (54). Other studies (55),(56) showed mixed results, making light of methodological concerns (insufficient sample sizes, decrease in compliance, lack of follow-up), whereby some researchers have rated the quality of evidence to be rather low (57) citing that it would be important to look at participants with different types and severity of dementia in future studies. A meta-analysis and systematic review by Du and colleagues (58) showed that exercise may improve cognitive function in AD and may potentially decelerate cognitive decline, however this relationship was not always found across studies. Therefore, the requirement for more RCTs with clear intervention criteria, larger sample sizes, and longer term fol-

low-up intervals are required to further elucidate the benefits of exercise on cognition in AD patients (58).

The ALMUTH study and Main Outcomes of the Current Article

The ALMUTH study was designed to further explore the potential benefits of music therapy and physical activity with the aim of decelerating the rate of brain aging in patients with a diagnosis of AD. For specific details of the ALMUTH protocol see the updated research study protocol (59).

The aim of the randomised pilot trial is to investigate if the inclusion of participants with AD into the ALMUTH protocol is feasible, and if continued recruitment of AD patients is warranted. The current pilot trial was conducted in conformance with the conceptual framework described by Eldridge and colleagues (60) known as the Consolidated Standards of Reporting Trials (CONSORT), in which parts of the future RCT are conducted on a smaller scale to determine the study's feasibility. Feasibility outcomes were therefore assessed to determine whether the pilot trial was feasible to continue recruitment and testing of AD patients.

Methods

Aim

The aim of this study was to examine the feasibility of the ALMUTH study in a group of mild-to-moderate AD patients and to determine if the 12-month intervention RCT protocol is feasible to conduct in such patients.

Trial Design

The study was conducted as a parallel three-arm randomised (1:1:1) controlled trial. The study was conducted in Bergen, Norway, where repeated assessments at baseline, and after 12-month follow-up were completed. The study was also carried out in accordance with the CONSORT Extension to Pilot and Feasibility Trials (60), with ClinicalTrials.gov identifier NCT03444181.

Research Setting

Neuropsychological testing and neuroimaging was undertaken at Haukeland Hospital and at the Department of Biological and Medical Psychology at the University of Bergen in Norway. Physical training sessions were undertaken at the Western Norway University of Applied Sciences sports facility. MT (singing lessons and twice monthly choir sessions) were delivered by registered music therapists at two locations in Bergen. Participants with limited mobility had musical therapy sessions at their homes.

Recruitment

Recruitment was carried out from April 2018 to April 2019. Potential participants were telephone screened and subsequently invited for a pre-assessment where they provided informed consent by both the participant and their caregiver. Recruitment efforts included advertising in newspapers, physical and online brochures, physical flyers distributed in elderly day centres, doctors offices, hospitals, and shopping centres, and radio appearances. Efforts included dissemination of flyers and brochures to general practitioners in the Bergen municipality to distribute to patients. Information was shared with outpatient clinics, including the National Association for Public health, Bergen Dementia Association, Polyphonic institute, radio appearances on Norwegian Broadcasting Corporation (NRK), and to twenty-five elderly day centres in the Bergen municipality. Events about AD were attended, such as World Alzheimer Day, with information booths about the ALMUTH project as part of the Bergen Dementia Association.

Participants

Due to safety and ethical requirements, participants were accompanied by a caregiver during the pre- and post-assessment, and throughout the study. Written informed consent was provided by both the patient and caregiver. The caregivers corroborated patient health status, patient medication, and ensured the participant's continued adherence to the study protocol over the study period. Caregivers were also present during the pre- and post-assessment tests and corroborated I- and P- ADL responses by the patients.

Inclusion criteria involved the recruitment of participants with (1) Norwegian as their first language (2) had a medical diagnosis of Alzheimer's Disease (3) mild to moderate severity of AD, defined as MMSE score above 10 (24) (Moderate AD between 11 and 20: Mild AD between 21 and 30) (4) still living at home (5) able to provide informed consent (6) have an accompanying caregiver present, and (7) able to undertake MRI scanning. Participants who moved to a nursing facility during the intervention period were not excluded from the study.

Exclusion criteria for the study were the presence of (1) severe psychiatric disorders (Major Depressive Disorder, Bipolar Disorder, Schizophrenia, Psychotic Symptoms), (2) History of traumatic brain injury (3) Neurological disease (Multiple Sclerosis, Epilepsy) (3) Sensory disorders (including deafness or severe auditory impairments) (4) Physical Immobility or diagnosis of Parkinson's Disease (5) Vascular disorders (history of heart disease, heart attack, heart surgery, stroke), (6) Other Dementia types (i.e. Lewy body dementia, Fronto-Temporal Dementia, Vascular Dementia) (7) Claustrophobia (8) Participants with ferro-magnetic metal in the soft tissue of the body not compatible with MR scanning (9) Living in a residential aged care facility.

Intervention

The ALMUTH project collected Norwegian-speaking mild-to-moderate Alzheimer's Disease patients which were included in a 12-month RCT (weekly sessions up to 40 sessions over the course of 12-months). The study included neuropsychological testing and MRI measurements with repeated assessments at baseline, and after 12 months. MRI was performed with three different MR sequences: structural T1-weighted imaging, diffusion tensor imaging, and two resting-state functional MRI acquisitions (one with, and one without music listening, counterbalanced across participants). Subjects were randomised to three groups: passive control (no treatment) and two active treatments: physical activity and music therapy (specifically singing lessons). Intervention details can be found in the ALMUTH study protocol (59).

Music Therapy Intervention

Participants randomised to the MT intervention were offered weekly singing lessons by registered music therapists (and music therapy students under the supervision of a registered music therapist). Weekly sessions were designed by the music therapists in collaboration with the researchers. Participants received up to 40 individual 1-1 sessions (45-60 minutes each) of weekly MT over the course of 12 months. Songs were adapted to the participant's abilities and ranged across varying degrees of difficulty. Participants received recorded study materials (burned cds, and/or MP3 files) which they were instructed to practice 30 minutes daily. Music therapy sessions included warm-up exercises including breathing techniques, song practice, as well as passive listening to the participant's music of choice. Music therapists and students also led twice monthly choir sessions for participants in the music intervention where participants met in a group setting to perform musical songs taught to them by the music therapists. Choir sessions lasted for 45 minutes. The intensity levels ranged from low to moderate.

Physical Activity Intervention

Participants randomised to the PA intervention were instructed by registered physiotherapists and sports educated personnel with a background in physical activity for adults and seniors. Weekly sessions were designed by the PA group exclusively. For all subjects randomised to the PA group, up to 40 sessions (totaling 70-90 minutes per session) of weekly group interventions were offered over a 12-month period. Participants received printouts of daily physical activities which they were instructed to practice 30 minutes daily. Most participants had a friend or caregiver accompanying them and taking part in the activities. Physical activities were tailored to the intensity level each participant and taught to their caregiver in order to perform them in tandem. The intensity levels ranged from low to moderate.

Control Group

Patients allocated to the control group were asked to continue with their routines as usual and asked not to attend any other concurrent research studies during the course of their 12-month participation. After 12 months, all patients in the CON group were offered to participate free of charge in the MT or PA group sessions and were interviewed on their activity levels during the year.

Neuropsychological Testing and Magnetic Resonance Imaging

The standardised neuropsychological test battery included the following questionnaires: The Consortium to Establish a Registry for Alzheimer's Disease (CERAD; (62)) World List Memory Test, Lawton Activities of Daily Living (Instrumental and Personal) (I and P-ADL; (63)), Geriatric Depression Scale (GDS; (64)), Mini-Mental State Examination (MMSE-Norwegian Revised version (61),(65), a computerised version of the Finger Tapping Test (FFT), Stroop Task, specifically the Word Colour Interference Test (CWIT), stimuli from the Profile of Perception of Music Skills (PROMS) test, and the Short Physical Performance Battery (SPPB; (66)). Changes to the testing protocol were quickly implemented by the researches to include a replacement of the computerised version of the Stroop task by a paper version of the Delis-Kaplan Executive Function System's (D-KEFS; (67)) and the online version of the

mini-version of the Profile of Perception of Music Skills (mini-PROMS; (68)). Neuroimaging was conducted using three measurements: structural MRI (sMRI), diffusion tensor imaging (DTI), and functional MRI (fMRI) with a counterbalanced music listening and non-music listening acquisition. Instrumental music with six different music genres was selected by the researchers: pop, rock, classical, jazz, world, and folk music. Participants could then choose their favourite genre to listen to during the MR recordings.

Table 1 Neuropsychological and Neuroimaging Testing Flow

Tests	Duration (min)
CERAD world list	5
I- and P- ADL	4-7
World list delayed recall	5
GDS	5-10
MMSE	7-10
Stroop	5-7
FFT	5
mini-PROMS	20-30
SPPB	5
Neuroimaging	
sMRI	9
DTI	8
fMRI	14

Order of neuropsychological and neuroimaging assessments. Duration listed in minutes.

Sample Size Estimation

Formal sample size estimations are not typically required for pilot trials (69), however, as this pilot trial is part of the larger study intended solely for the inclusion of AD patients, the sample size was estimated for the larger scale ALMUTH study. Sample size estimation was conducted using G* Power. To reach a medium effect size (between Cohen's d = 0.5 and 0.8), an estimate of 35 participants per group

is adequate to reach 80 % power with a two-tailed significance level of 2.5 %. To account for attrition rates of 22.22%, estimates of 45 participants per group for a total of 135 study participants across three groups was calculated. The aim was to recruit 135 participants in the span of the first 12 months.

Table 2 Intervention protocol details for weekly treatment sessions during 12-months

Intervention arm	Activity	Session Length (min)	Frequency (/month)	Intensity Level
Physical Activity	Warm-up, individual and group-based PA, cool-down, indoor and outdoor training physical activity, Nordic walking	70-90	4	Low to moderate
Music Therapy	Warm-up, vocal exercises, practice of choir songs, music listening	45-60	4	Low to moderate
	Choir sessions	45	2	Low to moderate
Control Group	None	N/A	N/A	N/A

Non-pharmacological therapies in the ALMUTH study by activity type, session length (minutes), frequency of sessions (/month), intensity levels. N/A: Not Applicable.

Randomisation, Sequence Generation, and Allocation Concealment

Randomisation was conducted after participants were screened for eligibility, consent forms were signed, and MRI and neuropsychological tests were completed. The randomisation procedure (1:1:1) was done via computer generated randomisation sequence using the software R and concealed by an external researcher who was not directly involved with the patients. Block randomisation with randomly varying block sizes of 3 or 6 were used to ensure balance and unpredictability. After participant baseline tests and MR recordings were completed, randomisation results were sent by email to the re-

searchers who then contacted the participants by phone and allocated them to one of three groups: MT, PA, or CON.

Blinding

The ALMUTH study is an open label study and therefore both researchers and participants were aware of their group allocation after randomisation.

Statistical Analysis

Descriptive statistics were used to compare the three allocated groups. The study was conducted with the intention-to-treat principle, which means that all participants were analysed in the group to which they were randomised, regardless of whether they actually received the allocated intervention. All analyses were undertaken using SPSS version 26.0.0.0. (IBM, Armonk, New York, U.S.A.)

Feasibility Outcome Measures

The study would be deemed feasible if the study met or could potentially meet the criteria found in Table 3.

Table 3 Feasibility Outcome Measures and Target Values

	Target Values
1.	Recruitment rate over 11.25 subjects per month over the course of 12 months
2.	Recruitment target of 135 participants reached over the course of 12 months
3.	Recruitment costs approximately 100 EUR per subject
4.	Attrition rates less than 25% based on sample size calculations
5.	Differential attrition rates no less than 25% per study arm
6.	Retention rates over 75%
7.	Adherence/Compliance to protocol with at least 80% of attendance to weekly sessions
8.	Location, room sizes, and equipment were sufficient

9.	Completeness of data at least 90% complete for baseline and follow-up tests
10.	Acceptability of intervention by study personnel where no issues are raised by the staff
11.	Study fidelity adherence by staff and researchers following protocol closely

Target values for feasibility of ALMUTH study.

Results

Participants

Fifty-one participants were assessed for eligibility of which eighteen right-handed Norwegian AD patients (10 Male and 8 Female) with a mean age of 74.89 years (SD = 6.56) were randomised between April 2018 and April 2020. The participants had no previous ailments and had acquired an AD diagnosis by a physician. Demographic details at baseline can be found in Table 4 and a detailed flow chart detailing participant flow can be found in Figure 1.

Table 4 Demographic characteristics at baseline assessment

Baseline Characteristics	**Control Group n/N (%), (N=6)**	**Physical Activity n/N (%), (N=6)**	**Music Therapy n/N (%), (N=6)**
Demographics			
Age (mean (SD))	76.67 (8.38)	73.83 (5.49)	77.17 (6.05)
Gender			
Male	3/6 (50)	3/6 (50)	4/6 (66.67)
Female	3/6 (50)	3/6 (50)	2/6 (33.33)
Handedness			
Right	6/6 (100)	6/6 (100)	6/6 (100)
Left	0/6 (0)	0/6 (0)	0/6 (0)
Both	0/6 (0)	0/6 (0)	0/6 (0)
Years of Education (mean (SD))	13.33 (2.16)	17.17 (3.49)	13.17 (3.19)
Diagnosis based on MMSE cutoff			
Mild AD	5/6 (83.33)	4/6 (66.67)	5/6 (83.33)
Moderate AD	1/6 (16.67)	2/6 (33.33)	1/6 (16.67)

Self-Reported Medical History			
Hearing Deficit	2/6 (33.33)	1/6 (16.67)	3/6 (50)
Medication			
AD Medication	5/6 (83.33)	5/6 (83.33)	3/6 (50)
Blood Pressure	1/6 (16.67)	2/6 (33.33)	3/6 (50)
Anxiety	0/6 (0)	0/6 (0)	1/6 (16.67)
Sleeping	0/6 (0)	0/6 (0)	0/6 (0)
Cholesterol	2/6 (33.33)	0/6 (0)	2/6 (33.33)
Allergy	2/6 (33.33)	0/6 (0)	0/6 (0)
Metabolism	0/6 (0)	1/6 (16.67)	1/6 (16.67)
Antidepressants	2/6 (33.33)	1/6 (16.67)	0/6 (0)
Previous Ailments	0/6 (0)	0/6 (0)	0/6 (0)
Lifestyle characteristics and background			
Smoking *	1/5 (20)	1/4 (25)	4/4 (100)
Singing Alone	4/6 (66.67)	4/6 (66.67)	5/6 (83.33)
Singing in Public	4/6 (66.67)	4/6 (66.67)	2/6 (33.33)
Dance	3/6 (50)	4/6 (66.67)	4/6 (66.67)
Currently Physically Active	2/6 (33.33)	6/6 (100)	4/6 (66.67)
Grew up with Music in the home	4/6 (66.67)	6/6 (100)	5/6 (83.33)
Parents sung lullabies	4/6 (66.67)	6/6 (100)	3/6 (50)
Have pets	0/6 (0)	0/6 (0)	1/6 (16.67)

Demographic descriptive statistics at baseline. M = Mean, SD = Standard Deviation, n = sample number. * = Missing Data

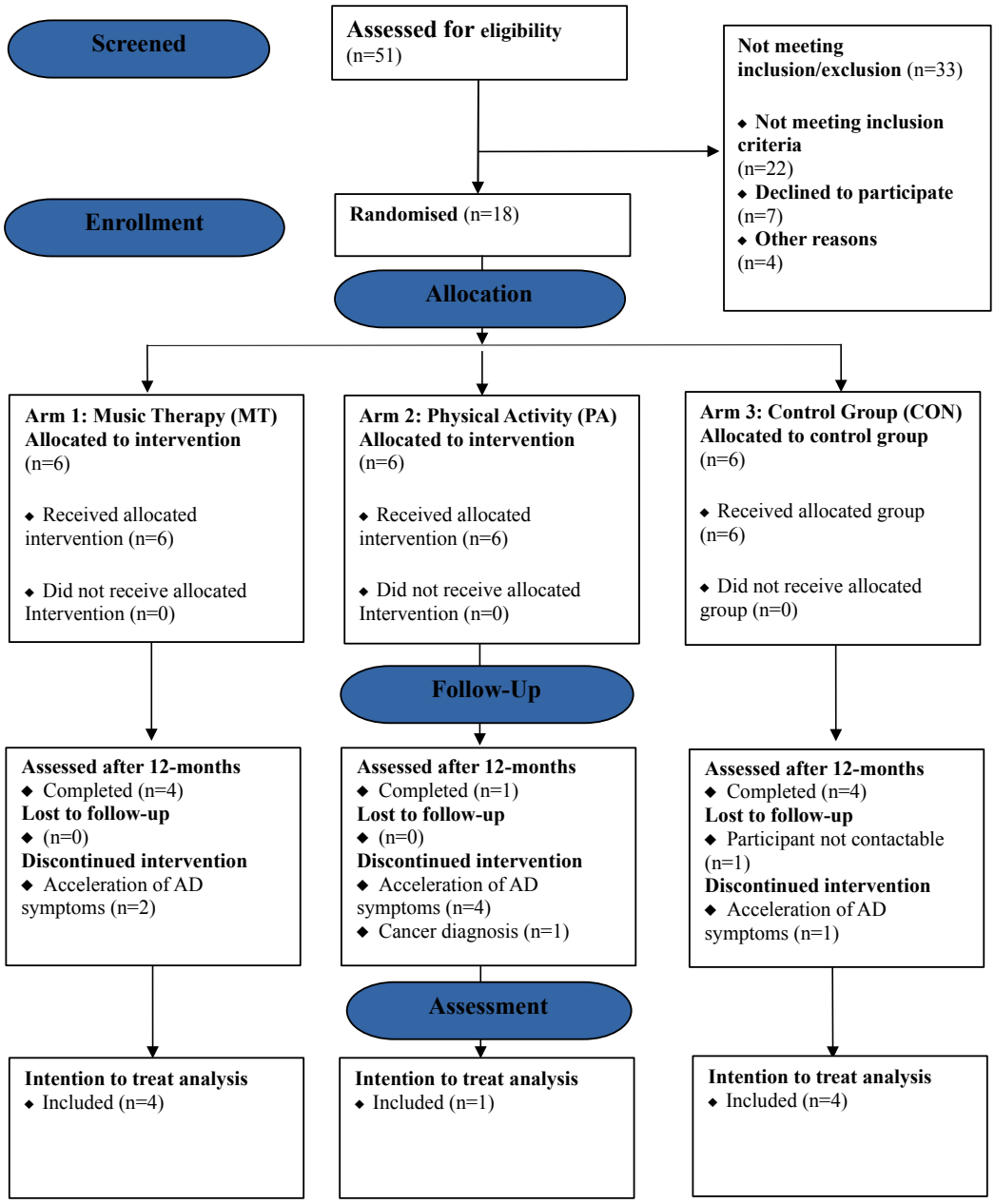

Figure 1. CONSORT diagram showing flow-through study for participants assessed for eligibility

Consent, Intention-to-Treat, and Harms: No issues were raised regarding consent by the participants and their caregivers. Consent was achieved by 100% of the patients and their caregivers. No participant who was randomised to a group deviated from their original group allocation. No adverse events were reported from the participants and/or caregivers.

Time requirements for recruitment and interventions

Recruitment and testing periods were set to be conducted between April 2018 and April 2020. Recruitment began between April 2018 and April 2019, while intervention sessions occurred over the course of 12-months after the initial pre-assessment date. The study sample size requirement of 135 AD participants was not reached during the initial recruitment period (April 2018 and April 2019). As the PA intervention began 8 months after the MT intervention, data was irregular and incomplete. Contractual PA agreements and organisational agreements were not finalised, delaying the timeline of the PA intervention start. This meant that of the six randomised individuals in the PA group, three of them were unable to attend any treatments and subsequently dropped out of the study.

Feasibility Outcomes

Table 5 Table of feasibility outcomes including targets values and actual values

Feasibility Outcome	**Target value**	**Actual value**
1. Recruitment Rate	> 11.25 subjects/month	1.5 subjects/month
2. Recruitment Total	135 subjects	18 subjects
3. Recruitment Costs	100 EUR per subject	500 EUR per subject
4. Retention Rates	> 75%	50%
5. Attrition Rates	< 25%	50%
6. Different Attrition Rates per study arm:		
I. MT	< 25%	2/6 (33.33%)

II. PA	< 25%	5/6 (83.33%)
III. CON	< 25%	2/6 (33.33%)
7. Adherence to Protocol	80% attendance	50%
8. Adequate Equipment	Room, Location, and Equipment are Adequate	Room, Location, and Equipment are Adequate
9. Data Completeness	> 90% Completeness	95.56%
10. Acceptability of Intervention by Staff	No issues raised by staff	Many issues raised by staff
11. Study Fidelity Adherence by Staff and Researchers	No study fidelity issues	Presence of study fidelity issues

Key feasibility assessments of target values and actual values reached.

1. Recruitment Rate

The recruitment of AD patients was conducted between April 2018 and April 2019. Eighteen eligible participants were randomised from a total of 51 telephone screened potential participants resulting in 35.29% of potential participants being randomised and booked for baseline assessments. The target goal was to recruit at least 11 subjects per month yet the actual value was approximately 1.5 subjects per month.

2. Recruitment Target Achieved

Recruitment of eligible, telephone screened, and randomised participants yielded 18/135 (13.33%) of the target goal of 135 patients over the course of 12-months.

3. Recruitment Costs

The initial advertisement budget was 14,000 EUR which accounted for approximately 100 EUR per 135 total projected participants. Recruiting costs for 18 participants cost a total of 9,000 EUR which amounted to 500 EUR per participant equivalent to five times the budgeted amount per individual.

4. Retention Rates

Target retention rates were over 75% retention of participants. Actual retention rates were 50% where 9/18 participants continued the intervention to completion and had follow-up tests 12-months later.

5. Attrition (Dropout) Rates

To account for attrition, estimates of 45 participants per group for a total of 135 study participants across three groups was calculated, accounting for about 22.22% total attrition rates (< 25%). Actual attrition rates were 50%, where 9/18 participants dropped-out due to the acceleration of AD symptoms, difficulty to contact participant, relocation to nursing homes, family members unable to continue due to the difficulty of the requirements of the study, and/or developed other illnesses like cancer. To ensure transparent reporting (70),(71), reasons for withdrawal can be found in Table 6.

Table 6 Reasons for withdrawal from ALMUTH study

Reasons for Withdrawal	**n/N, N=9**
Accelerating AD symptoms and AD progression	7/9
Caregiver unable to continue	5/9
Lived far away and unable to attend sessions	2/9
Other illnesses (i.e. cancer diagnosis)	1/9
Dissatisfied with the PA intervention	3/9
Unable to contact participant for follow-up	1/9

Of the nine participants who withdrew, several reasons were given, and the table shows how many complaints were made out of a total of the nine participant dropouts by the patients and/or their caregivers.

6. Differential Attrition Rates by Study Arm

To account for differential attrition rates, estimates of 45 participants per group for a total of 135 study participants across three groups was calculated (10 dropouts per group), accounting for about 22.22% attrition rates (< 25%). The differential attrition rate of the MT group was 2/6 (33.33%), followed by the PA group at 5/6 (83.33%), and the CON group 2/6 (33.33%). The PA group had more dropouts compared to the MT and CON groups. PA dropouts were mostly due to the PA intervention researchers not ready to begin the intervention until February 2019. Lateness to start the intervention in combination with accelerating AD symptoms contributed to the large dropout rates witnessed in the PA group.

7. Adherence to Protocol: Attendance Rates

Of the nine who completed the protocol, four of the nine were in the CON group. The one participant in the PA group attended 19 sessions, approximately 47.5% of the total offered sessions (up to 40 sessions total). The four MT participants joined anywhere from 8, 15, 21, and 40 sessions, which is equivalent to the participants joining approximately 52.5% of their total sessions during a year. Both the MT and PA groups combined allowed for a 50% global attendance to protocol. Adherence rates were set at 80% attendance in order to be included in the main analyses, however only one participant out of the five who completed an intervention had 100% adherence to the protocol.

Control participant activities during 12-months

CON group patients were instructed not to participate in any other studies over the course of the ALMUTH study and to continue with their regular routines over the course of the year. Participants were questioned during post-assessment about their activity levels during the year. Of the four CON participants who completed the ALMUTH protocol, one participant (allocated to the CON group) admitted to joining a three-month music therapy project. Three of the four did not deviate from their usual routine.

8. Adequate Equipment: Location, Room Size, and Equipment

The physical activity intervention was located at the Western Norway University of Applied Sciences sports facility. The facility was equipped for individual and group-based indoor and outdoor athletics, sports, and hiking. The music therapists acquired two rooms for the singing lessons to occur: a nursing home in Fyllingsdallen, Bergen and a room where the twice monthly choir sessions were also held in the city centre at Nordnes Bydelshus. Location, room size, and equipment were deemed sufficient across the intervention groups.

9. Data Completeness

The participants who completed pre- and post-assessments had a data completion rate of 95.56%.

10. Acceptability of Intervention by Staff

Issues faced by the physiotherapists and sports scientists:

In the physical activity group sessions, the sports scientists and physiotherapists found that the AD participants faced particular challenges in being able to move or cooperate with other participants without one or two students assisting them, and challenges connected to pharmaceutical side effects as rigidity and start/stop difficulties (parkinsonism). The main problem for a group-based intervention was therrapidly declining health of the participants, and the increased demand on manpower to run sessions (i.e. one or two helpers per participant). This affected group cohesion and did not allow for the creation of a sense of community between the participants, which also further limited the implementation of co-operative activities and/or games. Due to the heterogeneity of the participants, along with their rapidly declining health and functional status, it became difficult to meet individual demands and maintain group activities. Activity and intensity levels decreased which can have an affect on potential physical outcome (i.e. coordination, strength, endurance).

Issues faced by caregivers

In terms of additional operational issues, the physical therapy activities were conducted each Wednesday in the early evening at a gymnasium at the Western Norway University of Applied Sciences. Participants had to travel each week to the site. The PA sessions are dependent on their caregivers for transportation to the intervention location. Several caregivers struggled getting the participants to the sessions (i.e. getting dressed and ready, move out the door, getting into the car, driving to the facility, getting the patient out of the car and into the building). This struggle was repeated on the way home, and for an intervention of a 12-month long duration, this became burdensome on the caregivers. Some of the dropouts were due to caregivers being unable to meet the demands of the study. A study like ALMUTH must pay heed to what we expect from caregivers, even though a non-pharmacological therapy may show promise for ameliorating symptoms.

Issues faced by the musical therapists:

There were fewer issues to contend with in the musical therapy sessions as each session was individualised and based on more flexible appointment schedule that suited the participant (as opposed to the PA group that met every Wednesday). The musical therapist in some cases went to the homes of the participants who were unable to meet at the physical location where the music therapy sessions were held. Twice monthly choir sessions were held, however some spouses did not have time to bring the participants. Some did not enjoy having to go weekly to the choir sessions just to bring the participants back and forth.

11. Study Fidelity: Adherence by Researchers and Staff

Incomplete or missing subscale data and poorly administrated tests accounted for 28.89% of missing baseline data and was due to misconduct of a researcher who had discarded questionnaire data (SPPB, CERAD word list, MMSE, CWIT, and PROMS; this researcher was then removed from the project).

Most participants were unable to understand and had difficulty with the computerised version of the Stroop task and therefore the subsequent use of a paper version of the D-KEFS (67) was quickly implemented. Incorrectly coded stimuli taken from the PROMS was also replaced by the online validated version of the mini-PROMS (72).

Logistics for multi-site procedures were difficult to fully implement. Ideally, all collaborators would be organised and prepared to deal with an elderly demented population and have the necessary infrastructure ready. The music therapists were largely prepared and were consistent with intervention leading to more overall sessions completed by the music group. Due to insufficient funding and unforeseen planning difficulties, the physical activity was late to begin the interventions and were only able to begin eight months later (February 20, 2019). Both intervention partners and researchers were consistent throughout the study, keeping to the protocol closely, and were sensitive to the needs of the patients and their caregivers.

Discussion

Approximately 200 drug research and development projects in the last two decades have failed or have been abandoned (73) leading to overall concern that such studies are beginning too late during disease development. As the pathophysiological process of AD has been shown to begin years before the onset of clinical symptoms (78),(79), and due to established pathological burden (74), the focus on developing safe and effective interventions in early and presymptomatic AD stages has been encouraged (14). The same reasoning can be applied to the implementation of NPTs as early as possible. It is ethically critical and crucial to conduct feasibility assessments in research, particularly in disadvantaged populations like those with AD. The importance of performing pilot and feasibility studies not only informs larger trials (75), but is also used to test procedures that can be applied to the main study (76), and to

provide useful information across various processes required to implement such a trial (69). The randomised controlled pilot trial was conducted as a retrospective feasibility assessment of the ALMUTH study in order to optimise the quality of the trial and to determine if the strict inclusion of AD patients was feasible. Assessments of the feasibility criteria found that the pilot trial was not feasible exclusively in AD patients, and that the expansion into prodromal and preclinical stages would be more appropriate.

Limitations

In terms of the fidelity of the study, cooperation with research partners is both a limitation and a necessity. Good working partnerships and timely cooperation can expand research and knowledge, but improperly synchronised teams can create many difficulties for the management of such a large-scale project. Mishandled data was unfortunate, but was quickly rectified by the current researchers on the team and higher quality tests being swiftly implemented to make up for poorly administered tests (mini-PROMS and D-KEFS). For a large study of this duration, it would be necessary to ensure that enough personnel are hired, tasks equally divided, and budget costs allocated for replacement of staff if needed.

Due to unforeseen economic and planning needs, the PA partners were unable to begin offering sessions until February 2019, 8 months after the MT and CON groups began. This is a large limitation to our current study and has been since rectified in the expanded and upgraded version of the ALMUTH study (59). The length of the study also imposed considerable restrictions on the participants' adherence of the program as well as the family's ability to follow-up weekly implementation over such a long study period.

Advertising costs and unforeseen expenses due to the needs of the PA group revealed that it may be important to budget additional funds and that future studies wishing to implement similar large scale interventions with a particular diseased group should be wary of cost inefficiencies as well as recruitment difficulties, specifically in a small city like Bergen, Norway with nearly 300,000 inhabitants. In addition, the presence of competing research and university institutions also conducting concurrent studies on AD contributed considerably to the competition for access to the small sample pool of AD patients in Bergen. Furthermore, our research group did not have access to the hospital registry which other institutions had, making recruitment efforts more arduous and the discovery of available and eligible AD potential participants more difficult.

Future studies should be made aware of recruitment difficulties, poor participant retention and attrition rates, as well as concerns regarding follow-up assessments with patients who have progressed in their AD diagnosis. As studies have shown that brain changes occur decades before the presentation of the symptoms of AD (1), it would be prudent to begin in earlier stages as to be able to make the best use of NPTs. Thus, the chances for prevention or deceleration of cognitive decline appear to be best for milder forms of memory impairment. Moreover, studies aiming at preventing AD should focus on earlier or presymptomatic stages of the disease, while at the same time considering the costs to the participants and their families.

Generalisability

In preperation for similar future RCT studies assessing Alzheimer's Disease patients, the current randomised pilot trial may offer suggestions for further improvements and conduct. In regards to the ethics of pursuing such an RCT design with a disadvantaged group such as AD, it is suggested that a more flexible design may be undertaken whereby the participants are able to select the group of their

choosing which may enhance compliance and reduce dropout rates. As the RCT design is considered the gold standard for effectiveness in research (77), the study can include milder forms of memory impairments such as Mild Cognitive Impairment and Subjective Cognitive Decline, whereby the participants are healthier and may be able to adhere and better comply to the protocol of the study.

In the best interest of future studies, the use of an RCT design in a disadvantaged population who may not want to spend their remaining time complying to a randomisation procedure and be included in a group they may dislike may be noteworthy. Regarding the participants in the control group, it may be difficult for participants receiving a control group allocation during an otherwise very sensitive time in their disease progression, specifically when they are advised not to join any competing research projects during the allocated time they have consented to be included in a study. Although the nuances of joining a research project with an AD diagnosis may be specific to the individual, there is no doubt that the contribution of these participants is highly valuable, instructive, and has great benefit to the larger and complex issue of developing potential treatments for AD.

Empirical evidence suggests that regardless of intervention type, participants who adhere to the study till the end tend to do better than those who do not (78). Future studies may want to include a shorter intervention period (possibly 6 months in duration), or be aware of the difficulty in compliance and stamina required for such a demanding longitudinal study. Allowing participants to decide on their grouping may have helped to keep compliance to the study and adherence to the study protocol's requirements for daily practice and weekly attendance to therapy sessions. As each participant is required to join up to 40 sessions during a one year interval, the actual compliance rates to joining sessions was relatively low. Thus, low adherence and compliance to the study protocol can inform future studies not to be overly optimistic in their 'recruitment to completion' estimates.

Interpretation

According to Thabane and colleagues (69), there are four possible outcomes of a pilot study which can be found in Table 7.

Table 7 Interpretation of Pilot Study Outcomes

	Outcomes
1.	Stop: a main study is not feasible.
2.	Continue with study protocol modifications: main study is feasible but will require further modifications.
3.	Continue without modifications, but monitor carefully: main study is feasible but requires close attention.
4.	Continue without modifications: a main study is feasible and there is no further requirement to modify the protocol.

Four possible outcomes of a pilot study.

Reviewing the feasibility outcomes and based on the options in table 7, the randomised pilot trial falls under category 1 (Stop: a main study is not feasible). Reviewing the feasibility of such a longitudinal study in early phase AD patients, it is not recommended to further recruit AD patients for the AL-MUTH study or focus solely on AD recruitment in general.

Current amendments to the ALMUTH study

Taking account of the issues raised in the pilot trial, the ALMUTH study is currently recruiting subjects in preclinical and prodromal stages, such as participants with Mild Cognitive Impairment (MCI) (as diagnosed by a physician), Subjective Cognitive Decline (as categorised by the use of the Subjective Cognitive Decline Questionnaire (SCD-Q; (79), whereby both MyCog and TheirCog SCD-Q Scores are above 7), and participants claiming declining memory and who do not meet the criteria of the SCD-

Q (MyCog and TheirCog scores under 7) or are diagnosed with prodromal dementia. The ALMUTH study has also introduced an additional memory test which has been suggested for use by the International Working Group called the Free and Cued Selective Reminding Test (FCSRT; (80)-(81)). The FCSRT includes 16 pictorial stimuli which takes into account Immediate Recall, Free Recall, and Delayed Recall (also called pFCSRT + IR). Additional upgrades to the study include the inclusion of the revised Norwegian Dispositional Resilience Scale 15 items (DRS-15; (82)), the self-reported musical skills questionnaire (using two subscales: active engagement and musical training of the Goldsmiths Musical Sophistication Index (GOLD-MSI; (83)), and the addition of physical ability measures and caregiver assessments which can be found in detail in the revised study protocol (59).

Conclusion

Feasibility of the above randomised controlled pilot trial revealed that the ALMUTH protocol is not feasible in AD patients. The ALMUTH study in AD patients has also shown that it would be advantageous to begin active NPT interventions before clinical diagnosis of AD, and ideally before prodromal stages such as diagnosis of MCI due to AD, and other preclinical stages. The early implementation of an intervention study across earlier stages of memory decline offer a more constructive view on the efficacy of NPTs across a larger time scale. The updated ALMUTH protocol hopes to explore the effects of MT and PA on brain ageing in preclinical and prodromal stages of the AD continuum.

Supplementary Information

Abbreviations

ALMUTH: Alzheimer's and Music Therapy Study; AD: Alzheimer's Disease; CWIT: Colour Word Inteference Test; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CON: Control

group; D-KEFS: Delis-Kaplan Executive Function System's; DTI: Diffusion Tensor Imaging; DRS: Dispositional Resilience Scale; FCSRT: Free and Cued Selective Reminding Task; FFT: Finger Tapping Test; fMRI: Functional Magnetic Resonance Imaging; GOLD-MSI: Goldsmiths Musical Sophistication Index; MRI: Magnetic Resonance Imaging; MCI: Mild Cognitive Impairment; mini-PROMS: Mini-version of the Profile of Perception of Music Skills; MT: Music Therapy; NPTs: Non-Pharmacological Therapies; PA: Physical Activity; RCT: Randomised Controlled Trial; SPPB: Short Physical Performance Battery; sMRI: Structural Magnetic Resonance Imaging; SCD: Subjective Cognitive Decline

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Data and materials are available upon request.

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Consent for publications

All authors have consented to the publication of this research as presented in this manuscript.

Competing Interests

The authors declare that they have no competing interests.

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