Addition of a non-immersive virtual reality component to treadmill training to reduce fall risk in older adults (V-TIME): a randomised controlled trial

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SUMMARY

BACKGROUND

Age-associated motor and cognitive deficits increase the risk of falls, a major cause of morbidity and mortality. Because of the significant ramifications of falls, many interventions have been proposed, but few have aimed to prevent falls via an integrated approach targeting both motor and cognitive function. We aimed to test the hypothesis that an intervention combining treadmill training with non-immersive virtual reality (VR) to target both cognitive aspects of safe ambulation and mobility would lead to fewer falls than would treadmill training alone.

METHODS

We carried out this randomised, controlled trial at five clinical centres across five countries (Belgium, Israel, Italy, the Netherlands, and the UK). Adults aged 60−90 years with a high risk of falls based on a history of two or more falls in the 6 months before the study and with varied motor and cognitive deficits were randomly assigned by use of computer-based allocation to receive six weeks of either treadmill training plus VR or treadmill training alone. Randomisation was stratified by subgroups of patients (those with a history of idiopathic falls, those with mild cognitive impairment, and those with Parkinson's disease) and sex, with stratification per clinical site. Group allocation was done by a third party not involved in onsite study procedures. Both groups aimed to train three times per week for 6 weeks, with each session lasting about 45 min and structured training progression individualised to the participant's level of performance. The VR system consisted of a motion-capture camera and a computer-generated simulation projected on to a large screen, which was specifically designed to reduce fall risk in older adults by including real-life challenges such as obstacles, multiple pathways, and distracters that required continual adjustment of steps. The primary outcome was the incident rate of falls during the 6 months after the end of training, which was assessed in a modified intention-to-treat population. Safety was assessed in all patients who were assigned a treatment.

This study is registered with ClinicalTrials.gov, NCT01732653.

FINDINGS

Between Jan 6, 2013, and April 3, 2015, 302 adults were randomly assigned to either the treadmill training plus VR group (n=154) or treadmill training alone group (n=148). Data from 282 (93%) participants were included in the prespecified, modified intention-to-treat analysis. Before training, the incident rate of falls was similar in both groups (10·7 [SD 35·6] falls per 6 months for treadmill training alone vs 11·9 [39·5] falls per 6 months for treadmill training plus VR). In the 6 months after training, the incident rate was significantly lower in the treadmill training plus VR group than it had been before training (6·00 [95% CI 4·36−8·25] falls per 6 months; p<0·001 vs before training), whereas the incident rate did not decrease significantly in the treadmill training alone group (8·27 [5·55−12·31] falls per 6 months; p=0·49). 6 months after the end of training, the incident rate of falls was also significantly lower in the treadmill training plus VR group than in the treadmill training group (incident rate ratio 0·58, 95% CI 0·36−0·96; p=0·033). No serious training-related adverse events occurred.

INTERPRETATION

In a diverse group of older adults at high risk for falls, treadmill training plus VR led to reduced fall rates compared with treadmill training alone.

FUNDING

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INTRODUCTION

Gait impairments and falls are ubiquitous among older adults (roughly >65 years) and patients with many neurological diseases. About 30% of community-dwelling adults older than 65 years fall at least once per year.[1] Among people with mild cognitive impairment, dementia, or Parkinson's disease, falls are even more common with 60–80% of individuals reporting falls each year.[2] The consequences of falls often are severe, leading to loss of functional independence, social isolation, institutionalisation, disability, and death.[1] Falls also place a huge burden on health-care systems, accounting for 1−2% of all health-care expenditures in many high income countries.[3]

Most falls occur during walking[4] and hence gait impairment is associated with an increased fall risk.[5] Falls in elderly people often occur as a result of tripping and poor obstacle negotiation,[6] with the lower-leg of older adults passing dangerously close to impediments during walking.[7] Obstacle negotiation also relies on cognitive executive control, and judgment,8 partly explaining why age-related decline in cognitive function is associated with increased fall risk.[9]

Various intervention programmes have aimed to reduce fall risk.[10] However, despite the increasing recognition of the importance of cognition, motor, and obstacle negotiation abilities, previous multifactorial interventions have generally focused on individual risk factors separately, largely ignoring their interdependence. Cognition and motor aspects might both be targeted, but usually only individually. Growing evidence[11−13] and the increasing recognition of the importance of cognition for safe walking[14,15] suggest that a multimodal treadmill training programme augmented with a computer-simulated non-immersive virtual reality (VR) could improve both motor and cognitive aspects of fall risk.[16] Generally, VR is defined as a high-end-computer interface that involves realtime simulation and interactions through multiple sensorial channels.[16,17] Such an approach can be used to provide training in a stimulating and enriching environment that targets both motor and cognitive function, while also providing feedback about performance to assist with learning new motor strategies of movement. Integrated approaches that concurrently target motor and cognitive contributors to safe ambulation have not been well-studied. Consistent with existing recommendations,[10,18] we postulated that simultaneously training the motor and cognitive aspects of falls would help to reduce fall rates and ameliorate fall risk.

We aimed to test the hypothesis that a 6 week programme of treadmill training combined with a VR component would lead to a lower incidence of falls than would a similar intensity intervention delivered via treadmill training alone. We investigated this hypothesis in older adults at high risk of future falls based on a recent history of multiple falls, including people who had idiopathic falls, individuals with mild cognitive impairment, and people with Parkinson's disease.

METHODS

Study Design and Participants

We conducted a prospective, single-blind, randomised controlled trial, with 6 months follow-up at five clinical centres across five countries (Belgium, Israel, Italy, the Netherlands, and the UK; appendix). The trial was approved by the medical ethics review committee at each site. Details of the protocol and study design have been reported previously16 and additional details are available online.

We recruited community-living older adults via flyers, advertising, presentations at local residential and community senior centres, review of medical records at local outpatient clinics, and word of mouth. After initial screening by phone, chart review or interview, eligible individuals were invited to participate if they were aged 60−90 years, able to walk for at least 5 min unassisted, on stable medication for the past month, and self-reported two or more falls within 6 months before screening.[16] In addition to these criteria, individuals with mild cognitive impairment were included if they had a score of 0·5 on the Clinical Dementia Rating scale.[19] People with Parkinson's disease were included if they had been diagnosed in accordance with the UK Brain

Bank criteria, had Hoehn and Yahr stage II–III disease,[20] and were taking antiparkinsonian medication (to maximise patient homogeneity). Individuals were excluded if they had psychiatric co-morbidity (eg, major depressive disorder as in accordance with DSM IV criteria); history of stroke, traumatic brain injury or other neurological disorders (other than Parkinson's disease and mild cognitive impairment, for those groups); acute lower back or lower extremity pain; peripheral neuropathy; rheumatic and orthopaedic diseases; or a clinical diagnosis of dementia or severe cognitive impairment (Mini Mental State Exam [MMSE] score[21] <21). All decisions about eligibility were made before randomisation. After undergoing screening to confirm eligibility, individuals who agreed to participate in the study were asked to provide informed written consent.

Randomisation and masking

By use of computer-based allocation, participants were randomly assigned to receive either treadmill training plus VR or treadmill training alone. Due to the expected heterogeneity in fall rates, random assignment to training arm was stratified by subgroups of patients (ie, older adults with a history of falls, individuals with mild cognitive impairment, or people with Parkinson's disease). To ensure similar representation of men and women, randomisation was also stratified by sex. To minimise the effects of study site bias, all stratification procedures were done per clinical site. Allocation was done by the study contract research organization (Advanced Drug and Device Services [ADDS], Brno, Czech Republic), a third partly not involved in study procedures on site. Outcome assessors and monitors were masked to study group assignment.

Procedures

Participants aimed to train three times per week for 6 weeks in both groups, with each session lasting about 45 minutes. Training was similar between arms, except for the computerised simulation component for those subjects who were assigned to treadmill training plus VR. A trainer was present at all training sessions.

In the treadmill training plus VR intervention, the system included a camera for motion capture (a modified Microsoft Kinect for Windows, Microsoft, Redmond, WA, USA) and a computer generated simulation. The Microsoft Kinect camera was modified to include an additional camera to also distinguish between the feet. The camera recorded the movement of the participant's feet while they walked on the treadmill. These images were projected to the participant in real-time on a large screen during the training, enabling the participants to see their feet walking within the simulation. The virtual environment was specifically designed to reduce fall risk in older adults; it included real-life challenges, consisting of obstacles, multiple pathways, and distracters that necessitated continual adjustment of steps (figure 1).[11,16] The virtual environment imposed a cognitive load that demands attention, planning, dual tasking, response selection, and processing of rich auditory and visual stimuli that involve several perceptual processes. Visual and auditory feedback of performance and results were provided to participants both during training and as a summary at the end of the sessions. Training progression was structured in accordance with a prespecified plan for progression and was based on increasing both motor and cognitive challenges that were individualised to the participant's level of performance.[11,16] Progression of the intervention was modulated via the speed of the treadmill, the duration of the walking bouts within a given training session, and the size and frequency of the virtual obstacles and the distractors.

Treadmill training alone was chosen as the active control intervention because of its positive effect on mobility[22] and to allow for evaluation of the added value of the VR component. As in the treadmill training plus VR intervention, training progression was based on individual performance by increasing the duration of walking and walking speed in a standardised, prespecified fashion.[16] The amount of time spent with the trainer was similar to that in the experimental group and training followed similar guidelines, which detailed the time and steps to progression in a well-defined manner.

Fall rate was recorded during the 6 months after the end of training. A fall was defined as "an unexpected event in which the participant comes to rest on the ground, floor or lower level".[23] Because of the importance of this outcome, several options were provided for the recording of fall events and to maximise the accuracy of reporting. Participants received a falls calendar, which they were provided as a paper version, web-based calendar, or a smartphone application (appendix) in accordance with their preference. Information logged in the online or smartphone-based calendar was automatically uploaded to a database, whereas the paper calendars were posted back to the sites at which participants were recruited each month via pre-addressed envelopes. Research staff contacted all participants every month to maximise compliance. The falls database was checked, reviewed, and locked before intervention group assignment was unmasked.

Other outcomes were assessed at sessions 1 week before training and 1 week after training to examine acute effects, and 1 month and 6 months after training to examine retention effects. Gait speed and gait variability (using a Zeno instrumented walkway and PKMAS software, Havertown, PA, USA) were measured during usual walking and while participants negotiated physical obstacles. Inertial measurement units placed on both ankles and the lower back (Opal, APDM, Portland, OR,USA) were used to quantify foot clearance during obstacle negotiation.[24] Endurance was assessed with the 2 min walk test. The Short Physical Performance Battery (SPPB) was used to assess balance and mobility in the laboratory setting, whereas the Physical Activity Scale for the Elderly questionnaire was used to assess everyday activity.16 Attention and executive function were assessed by use of a computerised neuropsychological test battery (NeuroTrax Corp, Medina, Modiin, Israel).[25] Health related quality of life was measured with the SF-36 Health Survey. Disease severity in the patients with Parkinson's disease was classified in accordance with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS-III).[26]

All outcome measures (ie, falls and secondary outcome measures) were assessed by blinded assessors. Falls were recorded without knowledge of training group. An assessor at each site, who was masked to the intervention group allocation, did all assessments at roughly the same time of day to avoid variability of performance due to time or medication intake cycles. For the participants with Parkinson's disease, all tests were done in the practical self-reported on-medication state (roughly 1 h after medication intake).

Deviations from the original protocol[16] were widening of the age range from 60−85 years to 60−90 years to allow for inclusion of additional participants who could benefit from the interventions; lowering of the MMSE cutoff score from more than 24 to more than 21 to include participants with a wider range of cognitive impairments; and removal of the exclusion cutoff based on the New Freezing of Gait questionnaire, because the consortium realised that the existence of freezing of gait did not negate training.[27]

Outcomes

The primary outcome measure was the incident rate of falls in the 6 months after the end of training. Falls that occurred up to 182 days after training were included in the primary analysis. Secondary outcome measures investigated the effects of the interventions on known measures of fall risk, as previously reported.[16] These measures included gait speed and variability, foot clearance during obstacle negotiation, endurance, balance and mobility in the laboratory setting and in everyday activity, attention and executive function, and health-related quality of life. Additional secondary outcomes not reported in this Article include the effects of the interventions on the falls efficacy scale (FES-I), the Four Square Step Test, the mini-Balance Evaluation System Test, the Trail Making Test, verbal fluency, other measures of cognitive function (eg, memory), accelerometer-derived estimates of physical activity, and the user satisfaction questionnaire. Safety was assessed in terms of adverse events, which were defined as any untoward medical occurrence, unintended disease, or injury of the participants whether or not they were related to the intervention.[16]

Statistical analysis

Based on previous evidence,[28] we carried out an a-priori power analysis assuming that the fall incident rate after the intervention in the treadmill training alone group would be three falls per year. Assuming a 40%

reduction for the experimental group during the 6 month followup, [28] 166 participants (83 in each group) would be needed for 80% power to detect significant differences ($\alpha=0{\cdot}05$) between the treatment groups assuming non-inferiority with moderate correlation among covariates ($R^2=0{\cdot}50$). If we aimed for a more robust 90% power and assumed 20% loss to follow-up, we would need to recruit 137 participants per group. To enhance the ability to explore the effects of the intervention on fall incidence, we aimed to recruit 300 participants overall, distributed across the five study centres.

For the primary outcome, we estimated fall incident rates in the 6 months after training by use of negative binomial regression and a modified intention-to-treat analysis (appendix). The incident rate of falls and incident rate ratio (IRR), with 95% CIs, were calculated for comparisons between groups by use of negative binomial regression models. Training group was the fixed factor and the number of days after training with recorded falls data—ie, a measure of exposure—was an offset variable, therefore accounting for different observation periods for different participants. It is possible that participants reported more than one fall on a given day, but the model treated each participant with equal weights. Multiple falls on one day were counted as the number that occurred. We used age and sex as covariates because falls are more common in women and fall risk increases with age.[29–31] Baseline characteristics were compared between groups and we examined the effects of any characteristics that were marginally ($p<0.10$) different between the two groups. The level of significance was set at 5%. Prespecified secondary analyses assessed the change in falls status and explored the fall rates in the three subgroups of participants (ie, people with idiopathic falls, individuals with mild cognitive impairment, and people with Parkinson's disease). We analysed secondary outcome measures with generalised linear mixed-effects models (appendix). As prespecified, we checked the effect of study site in all of the primary and secondary analyses, by including site as a covariate; the effect was not significant and site was therefore not included in any of the final models (data not shown). We referred to the modified intention-to treat population used for the efficacy analyses as the full analysis set, which adhered as closely to the intention-to treat principle as was possible. The full analysis set included all participants who underwent randomisation, satisfied eligibility criteria, had at least three training sessions, and had any assessments during the 6 month follow-up period. According to the intention-to-treat principles, any participants who were randomly assigned to a group but discontinued the study before 6 months of follow-up were included into the full analysis set. Missing data resulting from dropouts, technical problems, and human errors were not imputed. The analysis plan was pre-specified in the protocol and the statistical analysis plan. The safety analysis included all participants who underwent randomisation and is presented as absolute and relative frequency counts, with comparisons between groups. All statistical analyses were done with SAS version 9.4. The contract research organisation, ADDS, conducted data monitoring and were also responsible for the database and for locking the database before unblinding.

This study is registered with ClinicalTrials.gov, number NCT01732653.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data. The corresponding author had final responsibility for the decision to submit for publication.

Results

661 individuals were screened. The most common reason for ineligibility was fewer than two falls in the 6 months before the study. Between Jan 6, 2013, and April 3, 2015, 302 participants were recruited who met the inclusion criteria, consented to participate, and were then randomly assigned to one of the training groups (148 to treadmill training alone and 154 to treadmill training plus VR). 16 (5%) participants dropped out before starting training, and four (1%) participants did not complete the minimum training sessions needed, leaving

282 participants (136 in the treadmill training alone group and 146 in the treadmill training plus VR group) who completed training and were included in the full analysis set (figure 2; appendix). Participants in the two training arms were well-matched with respect to baseline characteristics (table 1). The distribution of the three participant subgroups (130 with Parkinson's disease, 43 with mild cognitive impairment, and 109 people with idiopathic falls) was similar between the two groups (64 individuals in treadmill training group vs 66 in treadmill training plus VR group with Parkinson's disease; 20 vs 23 with mild cognitive impairment; and 52 vs 57 with idiopathic falls). The methods of reporting falls used by the participants were similar between groups (p=0·822; data not shown), as was compliance with the interventions (p=0·350); of 18 sessions, the mean number of completed sessions was 16·62 (SD 1·78) in the treadmill training plus VR group and 16·82 (1·81) in the treadmill training group. Overall, the falls incident rate before the intervention was 11·34 falls (95% CI 9·63−13·34) per 6 months.

Before training, incident rates were similar (p=0·29) between the training groups (table 2). After training, the incident rate for all participants was 7·10 falls (95% CI 5·51−9·14) per 6 months, which was a significant reduction compared with before training (p<0·0001). In the treadmill training plus VR group, the post-training incident rate was 6·00 falls (95% CI 4·36−8·25) per 6 months (p<0·001 compared with the 6 months before training). In the treadmill training group, the incident rate decreased to 8·27 falls (95% CI 5·55−12·31) per 6 months, but this reduction was not significant (p=0·49 compared with the 6 months before training). Similarly, the incident rate was lower after training in the treadmill training plus VR group than in to the treadmill training alone group (IRR 0·58, 95% CI 0·36–0·96; p=0·033; figure 3 and table 2), showing a significant advantage for treadmill training plus VR compared with treadmill training. Adjustment for MMSE scores did not affect the incident rate ratio (data not shown).

Before training, secondary outcome measures were similar) between the two training groups (table 3). Many of the secondary outcomes improved in both training groups after training, whereas other outcomes (gait speed variability, leading foot clearance, SPPB balance, SPPB gait, SF-36 physical total, and SF-36 mental total) improved more in the treadmill training plus VR group than in the treadmill training group (table 3).

Immediately after training, gait speed under usual and obstacle negotiation walking conditions improved (both p<0·0001) in both training groups. Gait variability during obstacle negotiation was significantly lower (ie, better) in the treadmill training plus VR group than in the treadmill training group. Obstacle clearance was greater after training in the treadmill training plus VR group than in the treadmill training group. Cognitive function outcomes improved similarly in both training groups. Scores on the SPPB also improved in both groups, however, significantly larger gains for the gait and balance components were achieved in the treadmill training plus VR group than in the treadmill training group. Conversely, self-reported daily life activity did not change after training in either arm (p=0·128 in treadmill training group; p=0·211 in treadmill training plus VR group).

Several measures were better in the treadmill training plus VR group than in the treadmill training group, even at the 6 month follow-up. These outcomes included endurance, obstacle clearance, mobility (ie, SPPB scores), and quality of life (table 3). Training effects at the end of training and the end of follow-up were generally larger in the treadmill training plus VR group among the patients with Parkinson's disease and the participants with idiopathic falls (effect sizes r=0·08–0·99); in the subgroup with mild cognitive impairment, the differences between treadmill training plus VR and treadmill training alone were less consistent, possibly because of the sample size (appendix). Variability in the Parkinson's disease group might be related to the differences in phenotype or disease manifestation within each of the groups.

28 adverse events were reported overall, with 24 occurring in participants who completed a minimum of three training sessions and were thus included in the analysis: all adverse events led to discontinuation. Of the 28 adverse events, there were five serious adverse events, which consisted of one death from natural causes (treadmill training group), one stroke (treadmill training plus VR group), one head injury resulting from a car

accident (treadmill training plus VR group) and two myocardial infarctions (treadmill training group). Minor adverse events included exacerbated orthopaedic-related pain or arthritis (four participants in the treadmill training plus VR group vs five in the treadmill training group), herpes-zoster (one vs zero), rhabdomyolysis (zero vs one), and pneumonia (one vs one). Eight participants sustained a fall during the training period, preventing them from returning to training. All of these falls occurred outside of the clinic, in the home or community (five participants in the treadmill training group vs three in the treadmill training plus VR group). All adverse events were investigated and none were deemed to be caused by the interventions. The frequency of these events was similar between the training arms (14 adverse events in each training group).

In prespecified exploratory analyses, we examined the falls incident rate after training in the three participant subgroups. Among the participants with Parkinson's disease, the incident rate was lower in the treadmill training plus VR group than in the treadmill training group (IRR 0·45, 95% CI 0·24–0·86; p=0·015) and this effect persisted after adjusting for disease severity (0·47, 0·25–0·89; p=0·021). Conversely, incident rate after training did not differ significantly between groups among the people with idiopathic falls (p=0·10) or the participants with mild cognitive impairment (p=0·99). The lack of effect among the people with idiopathic falls might be related to an imbalance in pretraining values (appendix).

We conducted a prespecified secondary analysis of falls status (ie, whether a participant had ≥2 falls in a given time period). Before training, all participants could be classed as having had multiple falls, as per the inclusion criterion of at least two falls in the 6 months before the study. After training, 171 (61%) of 282 participants reported no falls or only one fall and were therefore no longer classed as having multiple falls (table 2). This change in falls status occurred in all three subgroups and in both training groups (all p<0·0001). The greatest change in falls status was in subgroups of participants with mild cognitive impairment and the people with idiopathic falls; only 34 (22%) of these 152 participants (12 [28%] of 43 participants with mild cognitive impairment and 22 [20%] of 109 participants with idiopathic falls) had multiple falls during the 6 months after the intervention. Among the 130 participants with Parkinson's disease, 77 (59%) were defined as having had multiple falls after training, a significantly smaller proportion than before training (p<0·0001).

Results on the analysis of the additional secondary outcome measures (ie, FES-I, the Four Square Step Test, the mini-Balance Evaluation System Test, the Trail Making Test, verbal fluency, other measures of cognitive function, accelerometer-based estimates of physical activity, and the user satisfaction questionnaire) will be reported in future publications.

Discussion

To our knowledge, this study is the first to investigate the effects of an intensive treadmill-based intervention with and without a VR component on fall rates in an older adult population with a high risk of falls. Both treadmill training interventions significantly improved markers of fall risk and fall rates were lowered for both interventions compared with values from before training, emphasizing the therapeutic value of the active control intervention (ie, treadmill training alone). Nonetheless, comparisons within the training groups showed that the reduction in fall rates was only significant in the treadmill training plus VR group and not in the treadmill training group. Consistent with this finding, a direct comparison of the two training groups showed that the treadmill training plus VR intervention had a significant, positive effect on the incident rate of falls, the primary outcome, and fall risk (gait variability during obstacle negotiation and obstacle clearance), improving both to a larger degree than that seen in those who trained on the treadmill without the virtual reality component. In the treadmill training plus VR arm, the fall incident rate decreased from 11·92 falls per 6 months before training to 6·00 falls per 6 months after training, showing the ability of this multimodal approach to substantially reduce the number of falls in this high-risk population.

Many older adults are deconditioned, so it is not surprising that the intensive treadmill training was associated with improved outcomes in our high-risk participants, possibly by facilitating more effective motor control. This finding concurs with results from metaanalyses on the effect of exercise on fall risk in older adults and patients with Parkinson's disease.[28,33] Nonetheless, the rate of falls after training was 42% lower in the treadmill training plus VR arm than in the active control group of treadmill training alone. The added value of the VR component might be explained by the nature of the training. The motor-cognitive intervention provided by the VR implicitly trained obstacle negotiation strategies in a complex, enriched environment that requires focused attention and planning.[11] Executive function and attention have important roles in the regulation of gait, especially in complex situations such as obstacle negotiation.[34,35] Although the cognitive outcome measures were not sensitive enough to detect differences between training groups, everyday activities such as obstacle avoidance, which do require cognitive function, improved to a larger extent with the treadmill training plus VR intervention than they did with treadmill training alone. Training in the VR environment might have enhanced performance during attention demanding and challenging situations, thereby contributing to real-world fall avoidance during the 6 month follow-up period.

This observation is supported by the results of the secondary outcomes. After training, participants in the treadmill training plus VR group had lower (ie, better) gait variability during obstacle negotiation, and greater obstacle clearance than did those in the treadmill training group. Both gait variability and clearance amplitude are important measures of obstacle negotiation.[7,36] These are skills that could be regarded as training-specific gains, directly related to the intervention given that obstacle negotiation was trained in the VR. Still, it is important to note that participants were trained with virtual obstacles and the gains reported here were measured in the realworld, during over-ground walking. Most secondary outcomes improved in both training arms from before training to the end of training, reflecting the immediate training effects. However, retention effects were more common in the treadmill training plus VR group, especially for motor and motor-cognitive functions (eg, gait, obstacle negotiation, physical performance), suggesting that a learning effect might have contributed to the observed decrease in fall risk and fall frequency. This possibility is consistent with previously reported long-term training effects on fall risk achieved with other approaches.[37,38]

Results from several studies have shown that interventions that enhance cognitive skills lead to improvements in fall risk factors.[39,40] Additionally, subsequent studies have examined the use of combined motor-cognitive interventions to reduce fall risk in older adults, with conflicting findings. Eggenberger and colleagues[12] investigated the efficacy of two multicomponent cognitive–physical intervention programmes on fall risk mediators and fall frequency in older adults without cognitive impairments. Motor–cognitive training approaches were superior for improving fall risk mediators such as dual-task cost and gait variability compared with a similar intensity physical training intervention. However, they found no between-group difference in fall frequency at 6 months after the intervention. Fu and colleagues,[13] examined the effectiveness of the Wii Fit balance board (Nintendo, Kyoto, Japan) for reducing fall risk and incidence of falls in 60 nursing home residents. At 12 months after the intervention, the fall incidence rate was reduced in the group that trained with the Wii Fit balance board compared with a conventional exercise group, with the intervention showing efficacy even in frail older adults. Our findings are consistent with these preliminary observations and further support the notion that a combined motor-cognitive intervention could be beneficial to reduce fall rates in older adults and those with neurodegenerative conditions. Fu and colleague's findings and ours warrant further research and clinical implementation.

Our results suggest that treadmill training plus VR training has an advantage over treadmill training alone, especially in people with Parkinson's disease. For this subgroup, training with virtual reality reduced the risk of falls by nearly 60% (IRR 0·45) more than in the treadmill training intervention. This is noteworthy given the high fall rates in patients with this neurodegenerative disease.[2] It is possible that people with Parkinson's disease benefited most because their baseline rate of falls was highest. Another explanation could be that falls improved particularly in this subgroup because the pathophysiology of falls in Parkinson's disease usually involves the interplay between motor and cognitive deficits; both domains were clearly affected among the participants with Parkinson's disease in this study, and both domains were improved by the treadmill training plus VR training. By contrast, both training interventions reduced fall risk and improved falls status in the older adults and individuals with mild cognitive impairment subgroups. Possibly, the underlying cause of falls in these subgroups more heavily involved motor components and hence both treatment approaches were effective.

Alternatively, based on the lower reported fall frequency rate and better motor function compared with the participants with Parkinson's disease (appendix), the motor-cognitive training might not have been sufficiently tailored for these participants to produce differences between training groups in these two subgroups. Nonetheless, we wish to emphasise that although fall rates and falls status improved similarly in the treadmill training plus VR group and the active control group among the participants with mild cognitive impairment and individuals with idiopathic falls, there were still advantages to treadmill training with VR in terms of the effects on the fall risk measures (appendix). The relatively small sample size of individuals with mild cognitive impairment suggests that these subgroup-specific results need to be interpreted cautiously. It appears that the participants with idiopathic falls in both training groups benefited from the interventions, when comparing pretraining to post-training values with no differences between the training arms. However, it also seems that the rates of falls at baseline were different in this subgroup. Because of the inadequate power for the subgroup analyses and the problems of recall bias when using retrospective recall to estimate the number of falls over 6 months, it is possible that the lack of difference between the training arms truly reflects no added value for the VR on fall rates in this population or alternatively, this could be an artifact of the prebaseline differences in fall rates. This finding should be further explored.

The present study has several limitations. Both the experimental and control groups received active intensive treatment and we cannot assess the benefit of each treatment compared with no intervention. However, it is likely that a comparison to usual care would reveal an even larger impact given that usual care is often less intensive and focuses on general health, and few previous intervention studies have contrasted active interventions.[28] The study was not powered to detect differences between the two training arms in the subgroups. Thus, comparisons among the subgroups should be considered as being hypothesis-generating rather than hypothesis testing. Information about falls before training was based on a self-reported estimate for the previous 6 months, which introduces well-known recall bias.[41] To address this shortcoming, for the primary outcome, we compared differences between training arms based only on falls recorded after the intervention. Because of the nature of the study design, we cannot fully rule out the possible effect of regression to the mean on some of the secondary analyses and in the estimation of the reduction in fall rates compared to values before training. However, given that the participants in the two intervention arms were well-matched for all of the outcomes at baseline and that study participants were randomly allocated to comparison groups, the responses from both intervention arms were likely to be equally affected by regression to the mean. Questions about longer-term follow-up, the motor learning process during the training, and comparisons to other types of interventions need to be addressed in follow-up work. Future studies should also include a formal cost-benefit analysis. In the meantime, we note that the additional costs of treadmill training plus a VR component (<€4000 for a simple clinical setup) compared with treadmill training alone are minimal (the cost of the computer, screen, safety harness, and platform are relatively low for medium-income countries) and that treadmills are widely available. Although personalized supervision was used in the our study, such supervision is probably not necessary in everyday practice, for which group instruction might be sufficient, enabling highintensity, safe, and engaging training with minimal instructor assistance.[42] Additionally, it will be important to examine whether treadmill training plus VR can be used as part of a therapeutic prevention package to treat fall risk before falls become common and before any injuries occur. Although general exercise enhances cognition,[43] further investigation is also needed to better understand the similar effect of both training groups on cognition and whether improvements differ between subtypes of mild of cognitive impairment. However, the intervention was safe, the high retention rate (81%) shows the engagement and adherence of the subjects, and the very few adverse events that occurred were deemed to be unrelated to training. We found no differences between the five clinical sites, underscoring the fidelity of the approach used, its feasibility, and broad applicability. Finally, the inclusion of older adults with diverse characteristics supports the generalisability of this practical approach.

Contributors

AM, LR, MOR, BRB, EP, LA, GA, AN, and JMH participated in the conception, study design and obtaining of funding (FP7 EC consortium). IM, SDD, LA, FN, KD, and EB contributed to the data collection, data processing, interpretation of results, and drafting of the manuscript. AM and JMH contributed to the data analysis. AM, LR, MOR, BRB, EP, LA, GA, AN, NG, and JMH contributed to the interpretation of the results, drafting of the manuscript, and made critical revisions to the manuscript.

Declaration of interests

All authors report receiving support from the European Commission for the conduct of this study. LR also reports grants from NIHR HTA, Parkinson's UK, NIHR BRU, and the MRC, during the conduct of the study. BRB also reports personal fees from Danone, UCB, Adamas, TEVA, Zambon and Abbvie and grants from the National Parkinson Foundation, The Netherlands Organization for Scientific Research, Hersenstichting, the Michael J Fox Foundation, and Stichting Internationaal Parkinson Fonds, outside the submitted work. NG also reports personal fees from TEVA-Lundbeck, IntecPharma, NeuroDerm, Armon Neuromedical, Lysosomal Therapeutics, and Abviee, during the conduct of the study. AM, JMH, and NG report having submitted a patent application on the use of virtual reality, the intellectual property rights for which are held by the Tel Aviv Medical Center.

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AUTHORS CONTRIBUTIONS

AM, LR, MOR, BRB, EP, LA, GA, AN, and JMH participated in the conception, study design and obtaining funding (FP7 EC consortium). IM, SDD, LA, FN, KD and EB contributed to data collection, data processing, interpretation of results, and drafting the manuscript. AM and JMH contributed to the data analysis. AM, LR, MOR, BRB, EP, LA, GA, AN, NG and JMH contributed to the interpretation of the results, drafting of the manuscript, and made a critical revision of the manuscript.

DECLERATION OF INTERESTS

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Dr. Bloem also reports personal fees from Danone, UCB, Adamas, TEVA, Zambon and Abbvie and grants from the National Parkinson Foundation, The Netherlands Organization for Scientific Research, Hersenstichting, Michael J Fox Foundation and Stichting Internationaal Parkinson Fonds outside the submitted work.

Dr. Giladi also reports personal fees from TEVA-Lundbeck, IntecPharma, NeuroDerm, Armon Neuromedical, Lysosomal Therapeutics and Abviee, during the conduct of the study.

Dr's. Mirelman, Hausdorf and Giladi report having submitted a patent application on the use of virtual reality. The intellectual property rights for this patent application are held by the Tel Aviv Medical Center.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and the Cochrane Database for relevant articles published from Jan 1, 1980, to Dec 31, 2015. We used the keywords falls, prevention training, aging, older adults, and Parkinson's disease. The search resulted in the identification of several reviews and meta-analyses. Many intervention programs based on reported multiple risk factors have been proposed and evaluated. However, despite the extensive knowledge on fall risk obtained in recent years, there is no consensus as to the most efficacious or optimal treatment approach. To date, the impact on fall risk from common treatment approaches tends to be small and the reported changes are largely focused on motor aspects with limited long-term retention. Furthermore, most trials compared a fall prevention intervention with no intervention or an intervention not expected to reduce falls, stressing the need for studies with an active control comparison. A paucity of studies targeting participants with cognitive deficits was also noted. In addition, recent work on the role of the central nervous system in mobility calls for multi-modal interventions that target multiple pathways simultaneously, using an adaptive and individually tailored treatment in an enjoyable and challenging environment to increase adherence and maintenance. The present study addresses these gaps in previous fall risk interventions.

Added value of this study

This study is the largest randomized control trial conducted using a multi-modal, motor-cognitive training paradigm with virtual reality to reduce falls in older adults. Advantages of this approach include the fact it provides training in a more engaging, stimulating and enriched environment than traditional rehabilitation, gives feedback about performance to the subject to facilitate the learning of new motor strategies of movement, and simultaneously and seamlessly addresses motor and cognitive aspects of fall risk that are critical to safe ambulation. The multi-modal approach is compared to an active comparison intervention, namely a matched treadmill training program but without virtual reality. The results showed that treadmill training alone and treadmill training with virtual both reduced the risk of falls. At the same time, the multi-modal, motor-cognitive training approach decreased falls and fall risk to a larger degree than that seen in the active control comparison group.

Implications of all available evidence

Falls are wide-spread and common among older adults. There is, however, ample evidence that fall rates and risk can be reduced, even among older adults with an especially high risk of falls, such as people with Parkinson’s disease. Multi-modal therapies that target motor and cognitive function may have further added value, beyond an intervention that focuses on motor control alone. Interventions that combine technology, mobility training, and cognitive remediation to reduce the risk of falls and enhance mobility can apparently reduce fall rates and fall risk among the elderly, even among those with chronic disease and cognitive deficits. Targeting cognitive aspects of safe ambulation together with mobility using treadmill training is feasible, with minimal added costs compared to treadmill training alone, and with high levels of compliance, even in patients with neurodegenerative diseases and other high-risk populations, supporting a possible broad clinical translation of the results. A game-like approach based on virtual reality can apparently be applied to engage subjects, motivate compliance, and reduce fall rates in a diverse group of older adults.

Table 1: Subject characteristics*

	TT (n=136)	**TT+VR (n=146)**	**P-value**
Age [yrs]	73·3±6·4 73·0 (61·0 - 89·0)	74·2±6·9 74·0 (60·0 - 89·0)	0·244
Gender [M / F]	84 / 52 61·8% / 38·2%	98 / 48 67·1% / 32·8%	0·625
Education [yrs]	12·9±3·9 13·0 (3·0 - 30·0)	13·1±4·00 13·0 (5·0 - 22·0)	0·671
Fall history [number of falls in 6 months prior to the intervention]	10·7±35·6 2·5 (2·0 - 260·0)	11·9±39·5 3·0 (2·0 - 300·0)	0·786
Mini Mental State Examination [max 30]	28·2±1·7 28·5 (24·0 - 30·0)	27·8±1·8 26 (22·0 - 30·0)	0·092
Number of Prescription Medications	6·1±3·5 6 (1-19)	6·3±3·9 5 (1- 20)	0·703
Gait speed during 2 Minute Walk test [m/sec]	1·02±0·27 1·04 (0·21- 1·70)	1·02±0·28 1·04 (0·21- 1·70)	0·662

*Entries are Mean±SD and Median (Min-Max) or n and %. The number of prescription medications was used as a proxy for general health and is known to be associated with fall risk. P-values reported here are based on t-tests. See supplementary material Table 1 for the subject characteristics among the elderly fallers, the participants with MCI, and the people with PD.

Table 2: Secondary outcome measures prior to and after training

Domain	**Outcome measure**	**Assessment**	**TT**	**TT+VR**	**Difference of Least Square mean and CI LS mean (95% CI)**	**P value Arm**	**P value Time**	**P value Subgroup**
Gait	Gait speed usual walking (m/sec)	Pre-training	0·99	1·00	0·006 (-0·027, 0·004)	0·480	<0·001	0·005
		Post-training	1·07$^{\text{time}}$	1·06$^{\text{time}}$	-0·012 (-0·045, 0·022)			
		6M follow-up	1·05$^{\text{time}}$	1·05$^{\text{time}}$	-0·0003 (-0·035, 0·003)			
	Gait speed variability usual walking (%)	Pre-training	5·21	5·24	0·039 (-0·509, 0·588)	0·321	0·011	0·003
		Post-training	4·83	4·71$^{\text{time}}$	-0·121 (-0·673, 0·432)			
		6M follow-up	5·23	4·91	-0·609 (-1·194, -0·025)			
	Gait speed obstacle negotiation (m/sec)	Pre-training	0·94	0·95	0·003 (-0·031, 0·036)	0·320	<0·001	0·023
		Post-training	1·00$^{\text{time}}$	1·02$^{\text{time}}$	0·014 (-0·019, 0·048)			
		6M follow-up	0·98$^{\text{time}}$	0·98$^{\text{time}}$	0·022 (-0·014, 0·046)			
	Gait speed variability obstacle negotiation (%)	Pre-training	16·62	16·78	0·156 (-1·149, 1·461)	**0·018**	<0·001	0·020[3]
		Post-training	15·97$^{\text{time}}$	13·92$^{\text{time; arm}}$	-2·044 (-3·363,-0·725)			
		6M follow-up	14·84	13·90$^{\text{time}}$	-0·937 (-2·332, 0·456)			
	Leading foot clearance from obstacle during walking (cm)	Pre-training	32·38	32·22	-0·163 (-1·262, 0·934)	**0·002**	0·040	0·844[3]
		Post-training	32·03	33·74$^{\text{time}}$	1·244 (-0·055, 2·544)			
		6M follow-up	30·56$^{\text{time}}$	33·06$^{\text{arm}}$	2·498 (1·130, 3·867)			
	2 Minute walk test (m)	Pre-training	124·53	124·46	-0·730 (-4·057, 3·911)	0·077	<0·001	0·078[2,3]
		Post-training	128·48$^{\text{time}}$	132·49$^{\textbf{time; arm}}$	4·001 (0·011, 8·003)			
		6M follow-up	124·47	126·77	2·301 (-0·027, 9·536)			
Cognition	Executive function index	Pre-training	92·42	92·39	-0·252 (-1·973, 6·476)	0·398	<0·001	0·042
		Post-training	94·79$^{\text{time}}$	94·07$^{\textbf{time}}$	-0·722 (-2·277, 0·831)			
		6M follow-up	96·05$^{\text{time}}$	95·36$^{\text{time}}$	-0·701 (-2·327, 0·923)			
	Attention index score	Pre-training	91·83	91·57	-0·261 (-2·362, 1·838)	0·608	<0·001	0·034
		Post-training	93·63$^{\text{time}}$	93·26	-0·365 (-2·482, 1·752)			
		6M follow-up	94·86$^{\text{time}}$	95·12$^{\text{time}}$	0·257 (-1·958, 2·474)			
Mobility	Short Physical Performance Battery (SPPB) total	Pre-training	8·81	8·88	0·073 (-0·262, 0·410)	0·078	<0·001	0·054
		Post-training	9·46$^{\text{time}}$	9·61$^{\text{time}}$	0·151 (-0·186, 0·488)			
		6M follow-up	8·79	9·17$^{\text{arm}}$	0·377 (0·025, 0·729)			
	SPPB chair rise	Pre-training	2·04	2·07	0·033 (-0·159, 0·227)	0·992	<0·001	0·017
		Post-training	2·43$^{\text{time}}$	2·37$^{\text{time}}$	-0·059 (-0·252, 0·135)			
		6M follow-up	2·15	2·18	0·033 (-0·169, 0·236)			

	SPPB balance	Pre-training	3·22	3·23	0·003 (-0·176, 0·182)	**0·030**	<0·001	0·032^{3}
		Post-training	3·33$^{\text{time}}$	3·41$^{\text{time}}$	0·078 (-0·101, 0·258)			
		6M follow-up	3·09	3·39$^{\text{time; arm}}$	0·294 (0·106, 0·483)			
	SPPB gait	Pre-training	3·52	3·55	0·037 (-0·089, 0·164)	**0·032**	<0·001	0·238^{3}
		Post-training	3·68$^{\text{time}}$	3·80$^{\text{time; arm}}$	0·134 (0·007, 0·262)			
		6M follow-up	3·53	3·60	0·075 (-0·057, 0·208)			
	Physical Activity Scale for the Elderly (PASE)	Pre-training	101·7	102·8	0·988 (-9·023, 11·001)	0·126	0·281	0·410
		Post-training	95·8	102·2	6·350 (-3·793, 16·493)			
		6M follow-up	103·6	106·1	2·482 (-8·084, 13·049)			
Quality of Life	SF-36 Physical total	Pre-training	55·76	55·82	0·061 (-2·839, 2·962)	**0·033**	<0·001	0·008^{1}
		Post-training	57·73	60·56$^{\text{time}}$	2·768 (-0·171, 5·707)			
		6M follow-up	55·73	58·04	2·317 (-0·749, 5·383)			
	SF-36 Mental total	Pre-training	69·32	68·96	-0·358 (-3·280, 2·564)	**0·041**	0·072	0·494^{1}
		Post-training	70·43	72·35$^{\text{time}}$	1·924 (-1·037, 4·886)			
		6M follow-up	69·94	72·41$^{\text{time}}$	2·468 (-0·629, 5·567)			

For the sake of brevity, results at the 1 month time point are not shown. In general, values at this time point were in between those measured at the post and 6 month testing assessments. Pre-training, these secondary outcome measures were similar in the TT+VR and TT arms (p>0·12). The three p-values in the right most columns indicate main effects for training arm, time, and subject subgroup (e.g., MCI vs. PD) for each of the outcome measures. *1,2,3 indicate significant changes observed within the elderly, MCI or PD subgroups, respectively. SPPB: Short Physical Performance Battery. Values entered are the age and gender corrected least squares estimates of the mean. MCI: mild cognitive impairment; PD: Parkinson's disease; CI: confidence interval. For the SF-36, the summary indices for physical and mental health are reported. A significant arm X time interaction effect was observed for leading foot clearance. This measure became worse (smaller) in TT and better in TT+VR after training. $^{\text{time}}$ indicates a significant within training arm effects of time, compared to pre-training values. $^{\text{arm}}$ indicates a significant effect of TT+VR vs. TT.

Table 3: Falls incident rates in the 6 months prior to training and the 6 months post-training among all study participants and within each subgroup.

		Pre-training				**Post-training**			
		All subjects	**Elderly**	**MCI**	**PD**	**All subjects**	**Elderly**	**MCI**	**PD**
Total # of falls	**TT**	1456	168	57	1231	1083	45	25	1013
	TT+VR	1741	460	76	1205	817	276	52	489
# and % of recurrent fallers (≥ 2)	**TT**	136 (100%)	52 (100%)	20 (100%)	64 (100%)	49 (36·0%)	8 (15·4%)	6 (30·0%)	35 (54·7%)
	TT+VR	146 (100%)	57 (100%)	23 (100%)	66 (100%)	62 (42·5%)	14 (24·6%)	6 (26·1%)	42 (63·6%)
Falls incident rate (95% CI)	**TT**	10·71 (8·51, 13·47)	3·23 (2·70, 3·86)	2·85 (2·20, 3·69)	19·23 (13·39, 27·64)	8·27 (5·55, 12·31)	0·89 (0·55, 1·44)	1·28 (0·58, 2·79)	16·48 (9·96, 27·29)
	TT+VR	11·92 (9·47, 15·01)	8·07 (5·67, 11·49)	3·30 (2·64, 4·14)	18·26 (12·79, 26·07)	6·00 (4·36, 8·25)	5·10 (2·65, 9·80)	2·35 (1·11, 4·96)	8·06 (5·55, 11·71)
IR comparison p-value	**TT vs. TT+VR**	0·29	**<0·001**	0·29	0·34	**0·03**	0·10	0·99	**0·01**

Figure 1: The V-TIME treadmill training with virtual reality (VR) system. The system includes a camera based motion capture (Microsoft Kinect) and a computer generated simulation. The camera (see the red rectangle) records the movement of the participant's feet (see the red rectangle) while walking on the treadmill. These images were transferred into the computer simulation and projected to the patient in real-time time on a large screen during training (see the red rectangle). The VR enables the simultaneous and implicit training of motor function and the cognitive control needed for safe ambulation including obstacle negotiation, dual tasking, and planning. Progression of the intervention is modulated by the speed of the treadmill, the duration of the walking bouts within a given training session, and the size and frequency of the virtual obstacles and the distractors. VR is defined as a "high-end-computer interface that involves real time simulation and interactions through multiple sensorial channels"11.

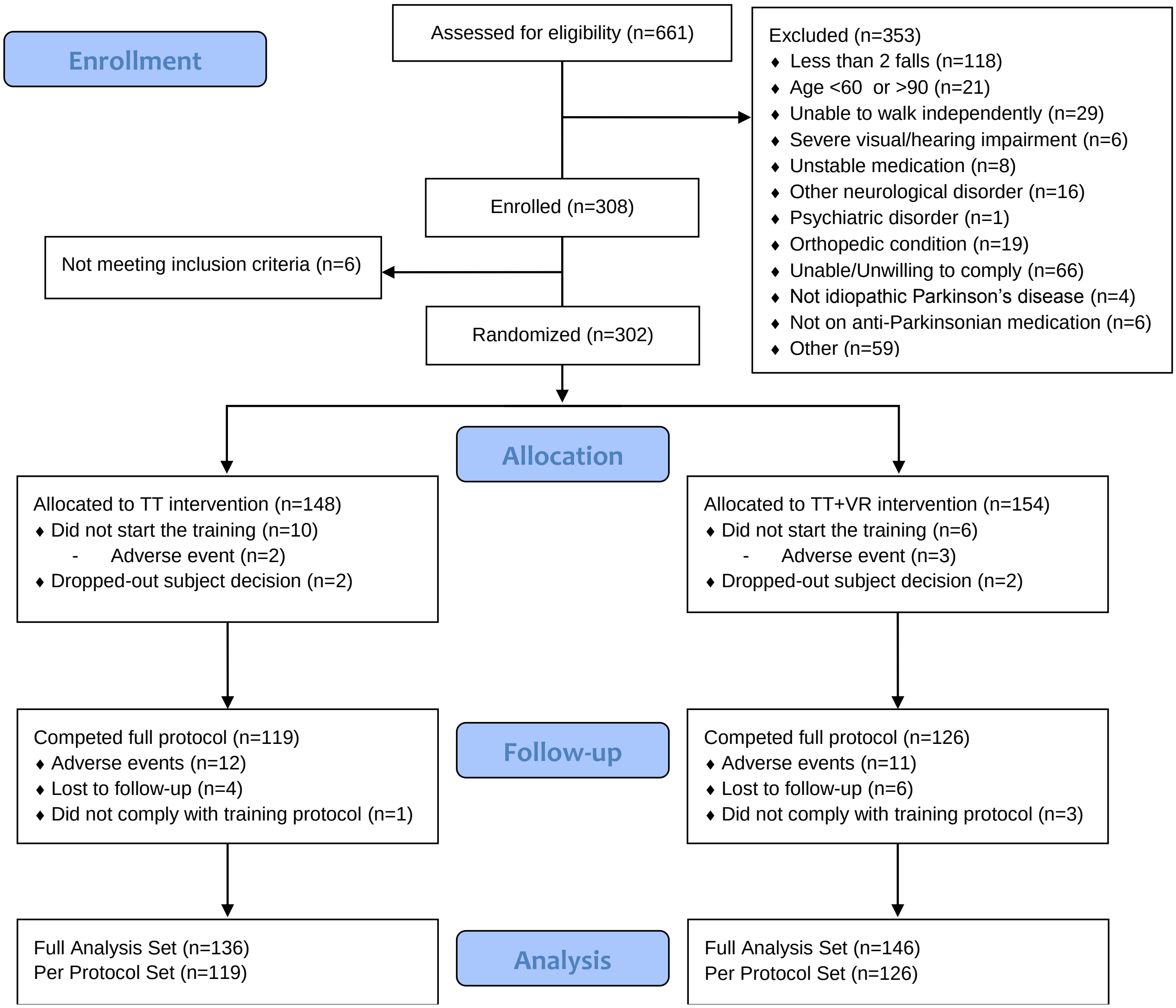

Figure 2: Flow of participants through the trial. 282 participants were included in the modified intention to treat analyses, (also known as Full Analysis Set – FAS) as reported in the Results (see SM for additional detail). Twenty participants are not included in the intention to treat analysis despite randomization; 16 subjects did not start training due to various reasons and 4 had less than 3 training sessions, and were excluded from the modified intention to treat plan, based on the the pre-specified analyses. 245 subjects completed the whole study period (i.e., complete training, assessments at each time point, and falls reporting) without major protocol deviations and formed the per-protocol data set. In this paper, all of the results reported are based on the pre-planned, modified intention to treat analyses. In general, the results for the per-protocol set were similar or slightly better than those in the intention to treat set. The first study subject was recruited in January of 2012. The last subject completed the final follow-up assessment in September of 2015.

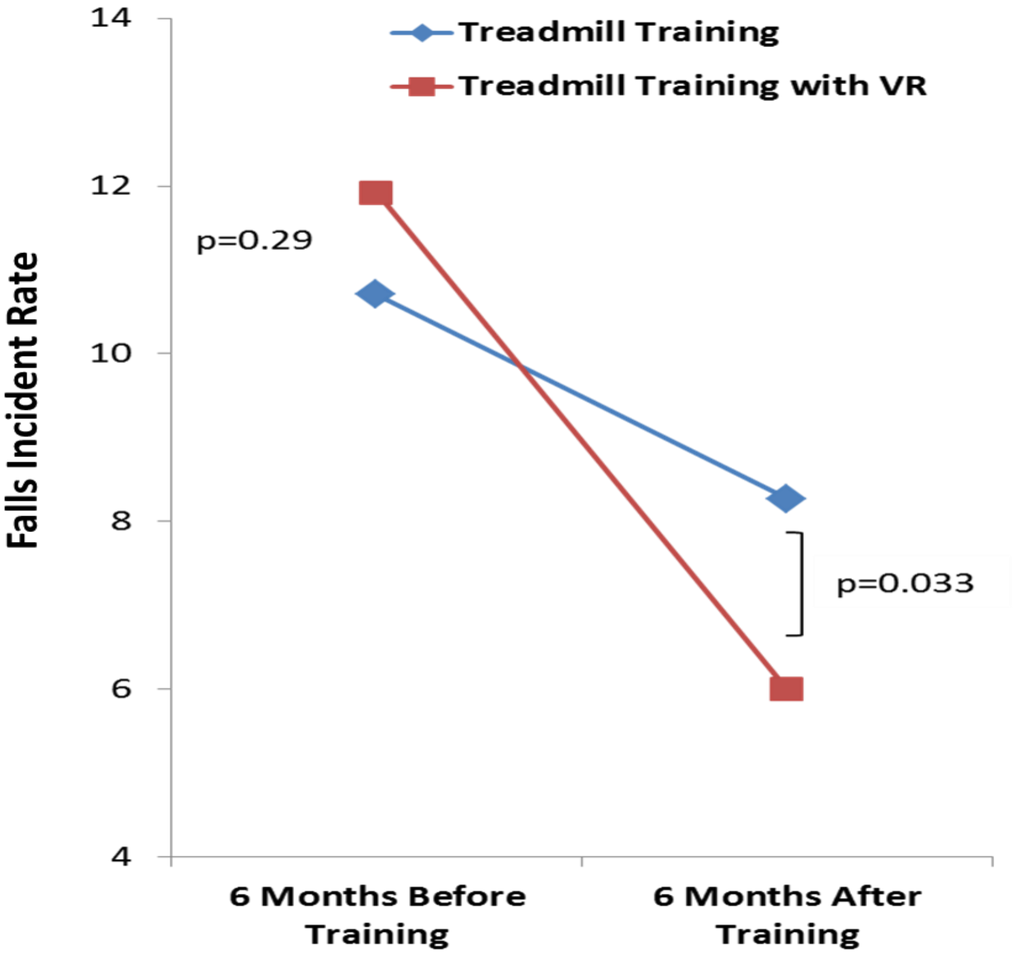

Figure 3: Differences in falls incident rates within and between training arms before and after training. Incident rates were similar in the treadmill training with virtual reality (TT+VR) and treadmill training (TT) arms pre-training. Subjects in both training arms had fewer falls post training, however, this decrease was significant only in the subjects in the TT+VR arm. Subjects in the TT+VR had 42% fewer falls during the 6 month follow-up period, compared to those in the TT arm (p=0.033). 95% confidence intervals and incidence rates for the subgroups are shown in Table 3.