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

Anat Mirelman, Lynn Rochester, Inbal Maidan, Silvia Del Din, Lisa Alcock, Freek Nieuwhof, Marcel Olde Rikkert, Bastiaan R Bloem, Elisa Pelosin, Laura Avanzino, Giovanni Abbruzzese, Kim Dockx, Esther Bekkers, Nir Giladi, Alice Nieuwboer, Jeffrey M Hausdorff

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 6 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<0·0001 *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 European Commission.

Published Online August 11, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31325-3

See Online/Comment http://dx.doi.org/10.1016/S0140-6736(16)31347-2

Center for the Study of Movement, Cognition and Mobility, Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (A Mirelman PhD, I Maidan PhD, Prof N Giladi MD, Prof J M Hausdorff PhD); **Department of Neurology** (A Mirelman, Prof N Giladi), **Department of Physical Therapy** (Prof J M Hausdorff), **Sackler Faculty of Medicine, and Sagol School of Neuroscience** (Prof N Giladi, Prof J M Hausdorff), **Tel Aviv University, Tel Aviv, Israel; Institute of Neuroscience, Newcastle University, Newcastle, UK** (Prof L Rochester PhD, S Del Din PhD, L Alcock PhD); **Department of Geriatrics Medicine** (F Nieuwhof MS, Prof M Olde Rikkert MD), **Radboud Alzheimers Center** (F Nieuwhof, Prof M Olde Rikkert), **and Department of Neurology** (F Nieuwhof, Prof B R Bloem MD), **Radboud University Medical Center, Donders Institute for Brain, Cognition and Behavior, Nijmegen, Netherlands; Department of Neurosciences** (E Pelosin PhD, L Avanzino MD, Prof G Abbruzzese MD) **and Department of Experimental Medicine** (L Avanzino), **University of Genoa, Genoa, Italy; and Department of Rehabilitation Sciences, Katholieke Universiteit Leuven, Leuven, Belgium** (K Dockx MS, E Bekkers MS, Prof A Nieuwboer PhD)

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

Correspondence to:
Dr Anat Mirelman, Center for the Study of Movement, Cognition and Mobility (CMCM), Neurological Institute, Tel Aviv Sourasky Medical Center, Tel Aviv 64239, Israel
anatmi@tlvmc.gov.il

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". We found several reviews and meta-analyses. Many intervention programmes based on reported multiple risk factors have been proposed and assessed. However, despite extensive knowledge about fall risk, no consensus exists as to the most effective or optimum treatment approach. To date, the effect of common treatment approaches on fall risk tends to be small and the reported changes are mainly focused on motor aspects with limited long-term retention. Furthermore, most trials have compared a fall prevention intervention with no intervention or an intervention not expected to reduce falls, showing the need for studies with an active control comparison. A paucity of studies targeting participants with cognitive deficits was also noted. Additionally, recent work on the role of the central nervous system in mobility calls for multimodal interventions that target multiple pathways simultaneously, using an adaptive and individually tailored treatment in an enjoyable and challenging environment to increase adherence and maintenance.

Added value of this study

To our knowledge, this study describes the largest randomised controlled trial to investigate use of a multimodal, motor-cognitive training approach with a virtual reality component for the reduction of falls in older adults. Advantages of this approach include the fact that it provides training in a more engaging, stimulating, and enriched environment than does traditional rehabilitation, gives feedback about performance to the participant to enable the learning of new motor strategies of movement, and simultaneously addresses motor and cognitive aspects of fall risk that are crucial to safe ambulation. We compared our multimodal approach with an active comparison intervention (a matched treadmill training programme) but without the virtual reality component, to better estimate the added effect of the virtual reality system. Our results showed that treadmill training alone and treadmill training with virtual reality both reduced the risk of falls. Furthermore, the approach with a virtual reality component reduced fall rate and fall risk to a greater degree than did the active control comparison group.

Implications of all available evidence

Falls are widespread and common among older adults. However, ample evidence suggests 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. Multimodal approaches that target motor and cognitive function might have added value on top of that from an intervention that focuses on motor control alone. Our results suggest that interventions that combine technology, mobility training, and cognitive remediation to reduce the risk of falls and enhance mobility can reduce fall rates and fall risk among the elderly, even among those with chronic disease and cognitive deficits. Targeting of both the cognitive aspects of safe ambulation and mobility aspects through treadmill training is feasible, with little added cost compared with treadmill training alone, and with high levels of compliance, even in patients with neurodegenerative diseases and other high-risk populations. A game-like approach based on virtual reality seems to be able to engage subjects, motivate compliance, and reduce fall rates.

resources, including motor planning, divided attention, 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 real-time 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.

 Published online August 11, 2016 http://dx.doi.org/10.1016/S0140-6736(16)31325-3

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 previously[16] 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 comorbidity (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 organisation (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 min. 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.

See Online for appendix

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 distractors 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.

For the more about the **V-TIME System** see http://www.v-time.eu/

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, pre-specified 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 calender, or a smartphone application (appendix) in

Figure 1: **Treadmill training with VR system**
The system includes a camera based motion capture (modified Microsoft Kinect) and a computer-generated simulation. The camera (red rectangle) records the movement of the participant's feet (the red rectangle) while they walk on the treadmill. These images are transferred into the computer simulation and projected to the patient in real time on a large screen during training (red rectangle). 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. Participants walked while wearing a safety harness to prevent falls during training. VR=non-immersive virtual reality.

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 follow-up,[28] 166 participants (83 in each group) would be needed for 80% power to detect significant differences (α=0·05) between the treatment groups assuming non-inferiority with moderate correlation among covariates (R^2=0·50). 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 in the full analysis set. Missing data resulting from dropouts, technical problems, and human errors were not imputed. The analysis plan was prespecified 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

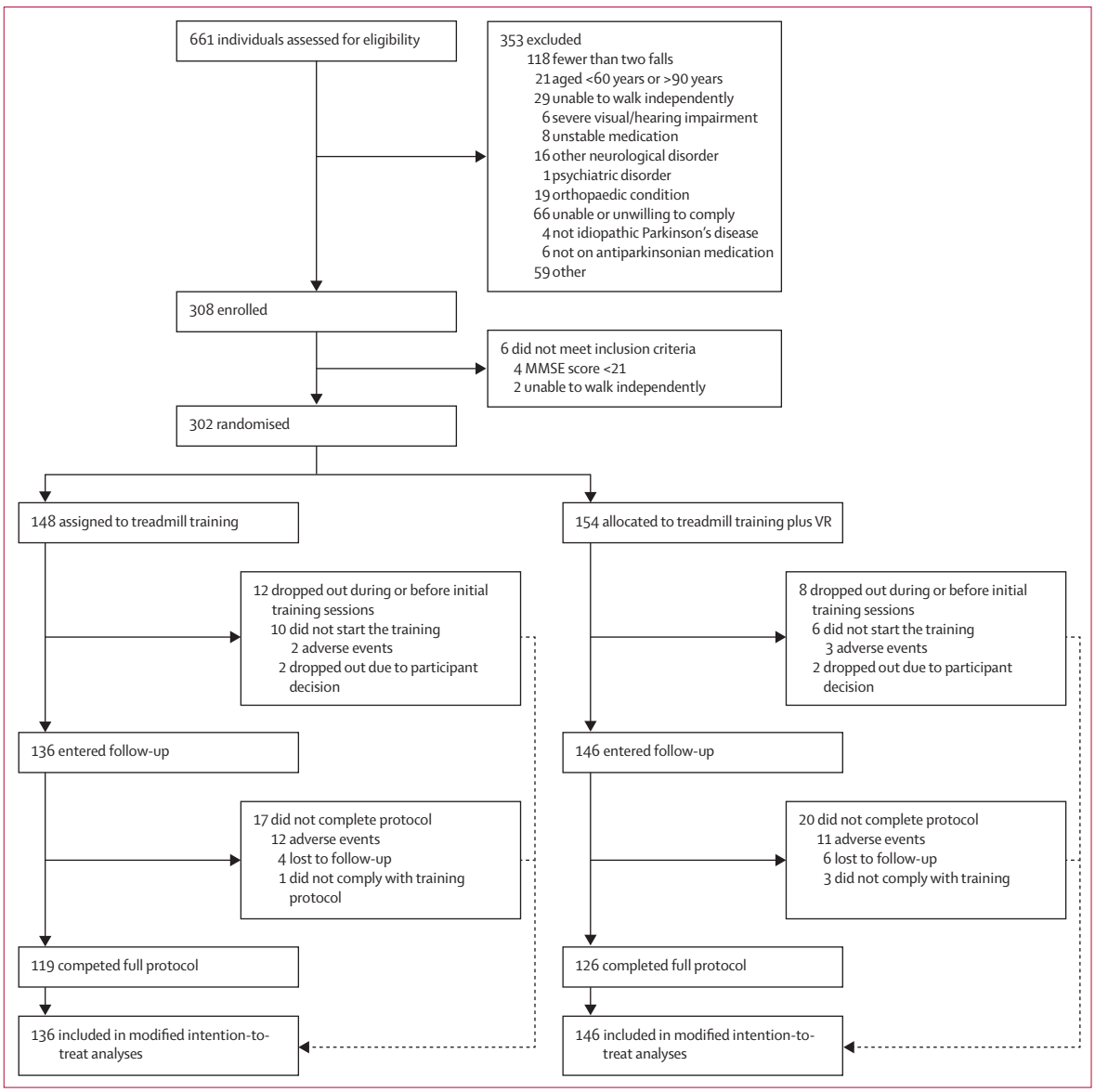

Figure 2: **Trial profile**
VR=non-immersive virtual reality. MMSE=Mini Mental State Exam.

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<0·0001 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 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 fall incident rate after training in the three participant

	Treadmill training (n=136)	Treadmill training plus VR (n=146)
Age (years)		
Mean (SD)	73·3 (6·4)	74·2 (6·9)
Median (IQR)	73·0 (68·0–78·0)	74·0 (69·0–80·0)
Sex		
Male	84 (62%)	98 (67%)
Female	52 (38%)	48 (33%)
Education (years)		
Mean (SD)	12·9 (3·9)	13·1 (4·0)
Median (IQR)	13·0 (10·0–16·0)	13·0 (10·0–16·0)
Fall history (number of falls in 6 months before training)		
Mean (SD)	10·7 (35·6)	11·9 (39·5)
Median (IQR)	2·5 (2·0–4·0)	3·0 (2·0–4·0)
Mini Mental State Examination score (out of 30)		
Mean (SD)	28·2 (1·7)	27·8 (1·8)
Median (IQR)	28·5 (27·0–30·0)	28·0 (27·0–29·0)
Number of prescription medications		
Mean (SD)	6·1 (3·5)	6·3 (3·9)
Median (IQR)	6·0 (4·0–7·0)	5·0 (4·0–7·0)
Gait speed during 2 min walk test (m/s)		
Mean (SD)	1·02 (0·27)	1·02 (0·28)
Median (IQR)	1·04 (0·80–1·20)	1·04 (0·80–1·20)

Data are mean (SD), median (IQR), or n (%). The number of prescription medications was used as a proxy for general health and is known to be associated with fall risk.[32] Characteristics for the subgroups of people who had falls, those with mild cognitive impairment, and those with Parkinson's disease are shown in the appendix. VR=non-immersive virtual reality.

Table 1: **Participant characteristics of the modified intention-to-treat population**

	6 months before training				6 months after training			
	All participants	People with idiopathic falls	Mild cognitive impairment	Parkinson's disease	All participants	People with idiopathic falls	Mild cognitive impairment	Parkinson's disease
Total falls								
Treadmill training	1456	168	57	1231	1083	45	25	1013
Treadmill training plus VR	1741	460	76	1205	817	276	52	489
People with ≥2 falls								
Treadmill training	136 (100%)	52 (100%)	20 (100%)	64 (100%)	49 (36%)	8 (15%)	6 (30%)	35 (55%)
Treadmill training plus VR	146 (100%)	57 (100%)	23 (100%)	66 (100%)	62 (42%)	14 (25%)	6 (26%)	42 (64%)
Incident rate of falls (95% CI)								
Treadmill training	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)
Treadmill training plus 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)
p value	0·29	0·0001	0·29	0·34	0·03	0·10	0·99	0·01

Data are n or n (%) unless otherwise specified. Fall status (ie, whether a participant had ≥2 falls) was a prespecified secondary analysis. VR=non-immersive virtual reality.

Table 2: **Falls in the 6 months before and after training**

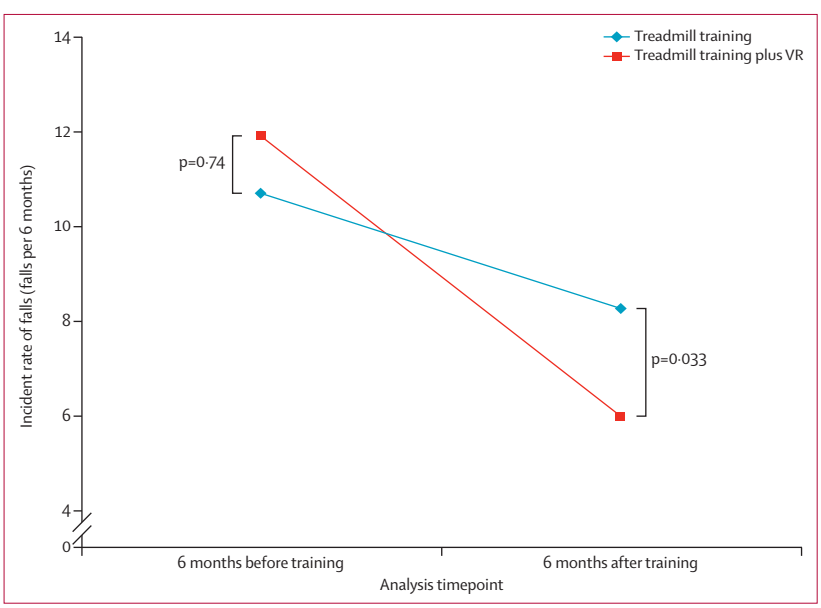

Figure 3: **Differences in fall incident rates within and between training groups before and after training**
95% CIs and incidence rates for the subgroups are shown in table 2. VR=non-immersive virtual reality.

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, the 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 fall 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 fall status occurred in all three subgroups and in both training groups (all p<0·0001). The greatest change in fall status was in the 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, emphasising

	Treadmill training	Treadmill training plus VR	Least square mean difference (95% CI)	p value (group)	p value (time)	p value (subgroup)
Gait						
Gait speed during usual walking (m/s)				0·480	<0·0001	0·005
Before training	0·99	1·00	0·006 (–0·027 to 0·039)	..	..	..
After training	1·07*	1·06*	–0·012 (–0·045 to 0·022)	..	..	..
6 month follow-up	1·05*	1·05*	–0·0003 (–0·035 to 0·003)	..	..	..
Gait speed variability during usual walking (%)				0·321	0·011	0·003
Before training	5·21	5·24	0·039 (–0·509 to 0·588)	..	..	..
After training	4·83	4·71*	–0·121 (–0·673 to 0·432)	..	..	..
6 month follow-up	5·23	4·91	–0·609 (–1·194 to –0·025)	..	..	..
Gait speed during obstacle negotiation (m/s)				0·320	<0·0001	0·023
Before training	0·94	0·95	0·003 (–0·031 to 0·036)	..	..	..
After training	1·00*	1·02*	0·014 (–0·019 to 0·048)	..	..	..
6 month follow-up	0·98*	0·98*	0·022 (–0·014 to 0·046)	..	..	..
Gait speed variability during obstacle negotiation (%)				0·018	<0·0001	0·020†
Before training	16·62	16·78	0·156 (–1·149 to 1·461)	..	..	..
After training	15·97*	13·92*‡	–2·044 (–3·363 to –0·725)	..	..	..
6 month follow-up	14·84	13·90*	–0·937 (–2·332 to 0·456)	..	..	..
Leading foot clearance from obstacle during walking (cm)				0·002	0·040	0·844†
Before training	32·38	32·22	–0·163 (–1·262 to 0·934)	..	..	..
After training	32·03	33·74*	1·244 (–0·055 to 2·544)	..	..	..
6 month follow-up	30·56*	33·06‡	2·498 (1·130 to 3·867)	..	..	..
2 min walk test (m)				0·077	<0·0001	0·078§†
Before training	124·53	124·46	–0·730 (–4·057 to 3·911)	..	..	..
After training	128·48*	132·49*‡	4·001 (0·011 to 8·003)	..	..	..
6 month follow-up	124·47	126·77	2·301 (–0·027 to 9·536)	..	..	..
Cognition						
Executive function index				0·398	<0·0001	0·042
Before training	92·42	92·39	–0·252 (–1·973 to 6·476)	..	..	..
After training	94·79*	94·07*	–0·722 (–2·277 to 0·831)	..	..	..
6 month follow-up	96·05*	95·36*	–0·701 (–2·327 to 0·923)	..	..	..
Attention index score				0·608	<0·0001	0·034
Before training	91·83	91·57	–0·261 (–2·362 to 1·838)	..	..	..
After training	93·63*	93·26	–0·365 (–2·482 to 1·752)	..	..	..
6 month follow-up	94·86*	95·12*	0·257 (–1·958 to 2·474)	..	..	..
Mobility						
SPPB total				0·078	<0·0001	0·054
Before training	8·81	8·88	0·073 (–0·262 to 0·410)	..	..	..
After training	9·46*	9·61*	0·151 (–0·186 to 0·488)	..	..	..
6 month follow-up	8·79	9·17‡	0·377 (0·025 to 0·729)	..	..	..
SPPB chair rise				0·992	<0·0001	0·017
Before training	2·04	2·07	0·033 (–0·159 to 0·227)	..	..	..
After training	2·43*	2·37*	–0·059 (–0·252 to 0·135)	..	..	..
6 month follow-up	2·15	2·18	0·033 (–0·169 to 0·236)	..	..	..
SPPB balance				0·030	<0·0001	0·032†
Before training	3·22	3·23	0·003 (–0·176 to 0·182)	..	..	..
After training	3·33*	3·41*	0·078 (–0·101 to 0·258)	..	..	..
6 month follow-up	3·09	3·39*‡	0·294 (0·106 to 0·483)	..	..	..
SPPB gait				0·032	<0·0001	0·238†
Before training	3·52	3·55	0·037 (–0·089 to 0·164)	..	..	..
After training	3·68*	3·80*‡	0·134 (0·007 to 0·262)	..	..	..
6 month follow-up	3·53	3·60	0·075 (–0·057 to 0·208)	..	..	..

(Table 3 continues on next page)

	Treadmill training	Treadmill training plus VR	Least square mean difference (95% CI)	p value (group)	p value (time)	p value (subgroup)
(Continued from previous page)						
Physical Activity Scale for the Elderly				0·126	0·281	0·410
Before training	101·7	102·8	0·988 (–9·023 to 11·001)	..	..	..
After training	95·8	102·2	6·350 (–3·793 to 16·493)	..	..	..
6 month follow-up	103·6	106·1	2·482 (–8·084 to 13·049)	..	..	..
Quality of life						
SF-36 Physical total				0·033	<0·0001	0·008¶
Before training	55·76	55·82	0·061 (–2·839 to 2·962)	..	..	..
After training	57·73	60·56*	2·768 (–0·171 to 5·707)	..	..	..
6 month follow-up	55·73	58·04	2·317 (–0·749 to 5·383)	..	..	..
SF-36 Mental total				0·041	0·072	0·494¶
Before training	69·32	68·96	–0·358 (–3·280 to 2·564)	..	..	..
After training	70·43	72·35*	1·924 (–1·037 to 4·886)	..	..	..
6 month follow-up	69·94	72·41*	2·468 (–0·629 to 5·567)	..	..	..

For brevity, results at the 1 month timepoint are not shown. p values represent the main effects of training group, time, and participant subgroup (ie, mild cognitive impairment *vs* Parkinson's disease *vs* people with idiopathic falls) for each of the outcome measures (preplanned secondary analyses). Values entered in the second and third columns are the age-and-sex corrected least squares estimates of the mean. For SF-36, the summary indices for physical and mental health are reported. SPPB=Short Physical Performance Battery. VR=non-immersive virtual reality. *Significant within-training-group effect of time compared with values before training. †Significant changes detected within the Parkinson's disease subgroup. ‡Significant effect of treadmill training plus VR compared with treadmill training alone. §Significant changes detected within the mild cognitive impairment subgroup. ¶Significant changes detected within the people who had idiopathic falls subgroup.

Table 3: **Secondary outcome measures before and after training**

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 meta-analyses 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 real world, during overground 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 multi-component 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 colleagues' 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 fall 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 fall 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 pre-training 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 set-up) 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 personalised supervision was used in the present study, such supervision is probably not necessary in everyday practice, for which group instruction might be sufficient, enabling high-intensity, 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, LAv, GA, AN, and JMH participated in the conception, study design, and obtaining of funding (FP7 EC consortium). IM, SDD, LAl, 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, LAv, 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 Abbvie, 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.

Acknowledgments

This work was funded by the European Commission (FP7 project V-TIME-278169). We thank all of the V-TIME participants and staff for their time and commitment to the study. We also thank the V-TIME technical partners who allowed for the success of this study, specifically, Stuart Cupit from Inition 3D technologies, Yoram Bar Zeev from Beacon Tech Limited, our colleagues from the University of Sassari in Sardinia, and the CRO Advanced Drug Development Services. All authors take responsibility for the accuracy and completeness of the reported data and vouch for the fidelity of the trial to the protocol.

References

1 Rubenstein LZ, Josephson KR. Falls and their prevention in elderly people: what does the evidence show? *Med Clin North Am* 2006; **90:** 807–24.

2 Wood BH, Bilclough JA, Bowron A, Walker RW. Incidence and prediction of falls in Parkinson's disease: a prospective multidisciplinary study. *J Neurol Neurosurg Psychiatry* 2002; **72:** 721–25.

3 Heinrich S, Rapp K, Rissmann U, Becker C, Konig HH. Cost of falls in old age: a systematic review. *Osteoporos Int* 2010; **21:** 891–902.

4 Robinovitch SN, Feldman F, Yang Y, et al. Video capture of the circumstances of falls in elderly people residing in long-term care: an observational study. *Lancet* 2013; **381:** 47–54.

5 Hausdorff JM, Rios DA, Edelberg HK. Gait variability and fall risk in community-living older adults: a 1-year prospective study. *Arch Phys Med Rehabil* 2001; **82:** 1050–56.

6 Ashburn A, Stack E, Ballinger C, Fazakarley L, Fitton C. The circumstances of falls among people with Parkinson's disease and the use of falls diaries to facilitate reporting. *Disabil Rehabil* 2008; **30:** 1205–12.

7 Galna B, Murphy AT, Morris ME. Obstacle crossing in people with Parkinson's disease: foot clearance and spatiotemporal deficits. *Hum Mov Sci* 2010; **29:** 843–52.

8 van Iersel MB, Kessels RP, Bloem BR, Verbeek AL, Olde Rikkert MG. Executive functions are associated with gait and balance in community-living elderly people. *J Gerontol A Biol Sci Med Sci* 2008; **63:** 1344–49.

9 Rosso AL, Studenski SA, Chen WG, et al. Aging, the central nervous system, and mobility. *J Gerontol A Biol Sci Med Sci* 2013; **68:** 1379–86.

10 Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society. Summary of the updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc* 2011; **59:** 148–57.

11 Mirelman A, Maidan I, Herman T, Deutsch JE, Giladi N, Hausdorff JM. Virtual reality for gait training: can it induce motor learning to enhance complex walking and reduce fall risk in patients with parkinson's disease? *J Gerontol A Biol Sci Med Sci* 2011; **66:** 234–40.

12 Eggenberger P, Theill N, Holenstein S, Schumacher V, de Bruin ED. Multicomponent physical exercise with simultaneous cognitive training to enhance dual-task walking of older adults: a secondary analysis of a 6-month randomized controlled trial with 1-year follow-up. *Clin Interv Aging* 2015; **10:** 1711–32.

13 Fu AS, Gao KL, Tung AK, Tsang WW, Kwan MM. Effectiveness of exergaming training in reducing risk and incidence of falls in frail older adults with a history of falls. *Arch Phys Med Rehabil* 2015; **96:** 2096–102.

14 Montero-Odasso M, Verghese J, Beauchet O, Hausdorff JM. Gait and cognition: a complementary approach to understanding brain function and the risk of falling. *J Am Geriatr Soc* 2012; **60:** 2127–36.

15 Yamada M, Aoyama T, Arai H, et al. Complex obstacle negotiation exercise can prevent falls in community-dwelling elderly Japanese aged 75 years and older. *Geriatr Gerontol Int* 2012; **12:** 461–67.

16 Mirelman A, Rochester L, Reelick M, et al. V-TIME: a treadmill training program augmented by virtual reality to decrease fall risk in older adults: study design of a randomized controlled trial. *BMC Neurol* 2013; **13:** 15.

17 de Bruin ED, Schoene D, Pichierri G, Smith ST. Use of virtual reality technique for the training of motor control in the elderly. Some theoretical considerations. *Z Gerontol Geriatr* 2010; **43:** 229–34.

18 Varma VR, Hausdorff JM, Studenski SA, et al. Aging, the Central Nervous System, and Mobility in Older Adults: Interventions. *J Gerontol A Biol Sci Med Sci* 2016; published online May 6. DOI:10.1093/gerona/glw080.

19 Morris JC. The Clinical Dementia Rating (CDR): current vision and scoring rules. *Neurology* 1993; **43:** 2412–14.

20 Goetz CG, Poewe W, Rascol O, et al. Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: status and recommendations. *Mov Disord* 2004; **19:** 1020–28.

21 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975; **12:** 189–98.

22 Mehrholz J, Kugler J, Storch A, Pohl M, Hirsch K, Elsner B. Treadmill training for patients with Parkinson's disease. An abridged version of a Cochrane Review. *Eur J Phys Rehabil Med* 2016; published online March 4.

23 Canning CG, Sherrington C, Lord SR, et al. Exercise for falls prevention in Parkinson disease: a randomized controlled trial. *Neurology* 2015; **84:** 304–12.

24 Trojaniello D, Cereatti A, Della CU. Foot clearance estimation during overground walking and vertical obstacle passing using shank-mounted MIMUs in healthy and pathological subjects. *Conf Proc IEEE Eng Med Biol Soc* 2015; **2015:** 5505–08.

25 Doniger GM, Simon ES. Computerized cognitive testing in aging. *Alzheimers Dement* 2009; **5:** 439–40.

26 Goetz CG, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): process, format, and clinimetric testing plan. *Mov Disord* 2007; **22:** 41–47.

27 Nieuwboer A, Rochester L, Herman T, et al. Reliability of the new freezing of gait questionnaire: agreement between patients with Parkinson's disease and their carers. *Gait Posture* 2009; **30:** 459–63.

28 Gillespie LD, Gillespie WJ, Robertson MC, Lamb SE, Cumming RG, Rowe BH. Interventions for preventing falls in elderly people. *Cochrane Database Syst Rev* 2003; **2003:** CD000340.

29 Dos Anjos RE, Saintrain MV, Pinheiro SS, et al. Falls in elderly adults- an analysis od injuries and sociodemographic conditions. *J Am Geriatr Soc* 2016; **64:** 891–93.

30 Sartini M, Cristina ML, Spagnolo AM, et al. The epidemiology of domestic injurious falls in a community dwelling elderly population: an outgrowing economic burden. *Eur J Public Health* 2010; **20:** 604–06.

31 Tinetti ME, Speechley M, Ginter SF. Risk factors for falls among elderly persons living in the community. *N Engl J Med* 1988; **319:** 1701–07.

32 Boyle N, Naganathan V, Cumming RG. Medication and falls: risk and optimization. *Clin Geriatr Med* 2010; **26:** 583–605.

33 Shen X, Wong-Yu IS, Mak MK. Effects of exercise on falls, balance, and gait ability in Parkinson's disease: a meta-analysis. *Neurorehabil Neural Repair* 2015; **30:** 512–27.

34 Brown LA, McKenzie NC, Doan JB. Age-dependent differences in the attentional demands of obstacle negotiation. *J Gerontol A Biol Sci Med Sci* 2005; **60:** 924–27.

35 Mak MK, Wong A, Pang MY. Impaired executive function can predict recurrent falls in Parkinson's disease. *Arch Phys Med Rehabil* 2014; **95:** 2390–95.

36 Heasley K, Buckley JG, Scally A, Twigg P, Elliott DB. Stepping up to a new level: effects of blurring vision in the elderly. *Invest Ophthalmol Vis Sci* 2004; **45:** 2122–28.

37 Morris ME, Menz HB, McGinley JL, et al. A Randomized controlled trial to reduce falls in people with parkinson's disease. *Neurorehabil Neural Repair* 2015; **29:** 777–85.

38 Pai YC, Bhatt T, Yang F, Wang E. Perturbation training can reduce community-dwelling older adults' annual fall risk: a randomized controlled trial. *J Gerontol A Biol Sci Med Sci* 2014; **69:** 1586–94.

39 Segev-Jacubovski O, Herman T, Yogev-Seligmann G, Mirelman A, Giladi N, Hausdorff JM. The interplay between gait, falls and cognition: can cognitive therapy reduce fall risk? *Expert Rev Neurother* 2011; **11:** 1057–75.

40 Verghese J, Mahoney J, Ambrose AF, Wang C, Holtzer R. Effect of cognitive remediation on gait in sedentary seniors. *J Gerontol A Biol Sci Med Sci* 2010; **65:** 1338–43.

41 Ganz DA, Higashi T, Rubenstein LZ. Monitoring falls in cohort studies of community-dwelling older people: effect of the recall interval. *J Am Geriatr Soc* 2005; **53:** 2190–94.

42 Shema SR, Brozgol M, Dorfman M, et al. Clinical experience using a 5-week treadmill training program with virtual reality to enhance gait in an ambulatory physical therapy service. *Phys Ther* 2014; **94:** 1319–26.

43 Öhman H, Savikko N, Strandberg TE, et al. Effects of exercise on cognition: the Finnish Alzheimer disease exercise trial: a randomized, controlled trial. *J Am Geriatr Soc* 2016; **64:** 731–38.