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[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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1  
2 **Addition of a non-immersive virtual reality component to treadmill**  
3 **training to reduce fall risk in older adults (V-TIME): a randomised**  
4 **controlled trial**

5 *The Lancet*

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## SUMMARY

40

41

### 42 BACKGROUND

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

### 49 METHODS

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

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

### 65 FINDINGS

66 Between Jan 6, 2013, and April 3, 2015, 302 adults were randomly assigned to either the treadmill training plus  
67 VR group (n=154) or treadmill training alone group (n=148). Data from 282 (93%) participants were included in  
68 the prespecified, modified intention-to-treat analysis. Before training, the incident rate of falls was similar in  
69 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  
70 treadmill training plus VR). In the 6 months after training, the incident rate was significantly lower in the  
71 treadmill training plus VR group than it had been before training (6·00 [95% CI 4·36–8·25] falls per 6 months;  
72  $p<0\cdot001$  vs before training), whereas the incident rate did not decrease significantly in the treadmill training  
73 alone group (8·27 [5·55–12·31] falls per 6 months;  $p=0\cdot49$ ). 6 months after the end of training, the incident rate  
74 of falls was also significantly lower in the treadmill training plus VR group than in the treadmill training group  
75 (incident rate ratio 0·58, 95% CI 0·36–0·96;  $p=0\cdot033$ ). No serious training-related adverse events occurred.

### 76 INTERPRETATION

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

### 79 FUNDING

80 European Commission (FP7 V-TIME-278169)

## 81 INTRODUCTION

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

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

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

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

113

## 114 METHODS

### 115 *Study Design and Participants*

116 We conducted a prospective, single-blind, randomised controlled trial, with 6 months follow-up at five clinical  
117 centres across five countries (Belgium, Israel, Italy, the Netherlands, and the UK; appendix). The trial was  
118 approved by the medical ethics review committee at each site. Details of the protocol and study design have  
119 been reported previously<sup>16</sup> and additional details are available online.

120 We recruited community-living older adults via flyers, advertising, presentations at local residential and  
121 community senior centres, review of medical records at local outpatient clinics, and word of mouth. After initial  
122 screening by phone, chart review or interview, eligible individuals were invited to participate if they were aged  
123 60–90 years, able to walk for at least 5 min unassisted, on stable medication for the past month, and self-  
124 reported two or more falls within 6 months before screening.<sup>16</sup> In addition to these criteria, individuals with  
125 mild cognitive impairment were included if they had a score of 0.5 on the Clinical Dementia Rating scale.<sup>19</sup>  
126 People with Parkinson's disease were included if they had been diagnosed in accordance with the UK Brain

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

135

### 136 ***Randomisation and masking***

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

145

### 146 ***Procedures***

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

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

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

171 Fall rate was recorded during the 6 months after the end of training. A fall was defined as “an unexpected  
172 event in which the participant comes to rest on the ground, floor or lower level”.<sup>23</sup> Because of the importance

173 of this outcome, several options were provided for the recording of fall events and to maximise the accuracy of  
174 reporting. Participants received a falls calendar, which they were provided as a paper version, web-based  
175 calendar, or a smartphone application (appendix) in accordance with their preference. Information logged in  
176 the online or smartphone-based calendar was automatically uploaded to a database, whereas the paper  
177 calendars were posted back to the sites at which participants were recruited each month via pre-addressed  
178 envelopes. Research staff contacted all participants every month to maximise compliance. The falls database  
179 was checked, reviewed, and locked before intervention group assignment was unmasked.

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

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

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

202

## 203 **Outcomes**

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

215

## 216 **Statistical analysis**

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

219 reduction for the experimental group during the 6 month followup,<sup>28</sup> 166 participants (83 in each group)  
220 would be needed for 80% power to detect significant differences ( $\alpha=0.05$ ) between the treatment groups  
221 assuming non-inferiority with moderate correlation among covariates ( $R^2=0.50$ ). If we aimed for a more robust  
222 90% power and assumed 20% loss to follow-up, we would need to recruit 137 participants per group. To  
223 enhance the ability to explore the effects of the intervention on fall incidence, we aimed to recruit 300  
224 participants overall, distributed across the five study centres.

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

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

253

### 254 ***Role of the funding source***

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

258

### 259 **Results**

260 661 individuals were screened. The most common reason for ineligibility was fewer than two falls in the 6  
261 months before the study. Between Jan 6, 2013, and April 3, 2015, 302 participants were recruited who met the  
262 inclusion criteria, consented to participate, and were then randomly assigned to one of the training groups  
263 (148 to treadmill training alone and 154 to treadmill training plus VR). 16 (5%) participants dropped out before  
264 starting training, and four (1%) participants did not complete the minimum training sessions needed, leaving

265 282 participants (136 in the treadmill training alone group and 146 in the treadmill training plus VR group) who  
266 completed training and were included in the full analysis set (figure 2; appendix). Participants in the two  
267 training arms were well-matched with respect to baseline characteristics (table 1). The distribution of the three  
268 participant subgroups (130 with Parkinson's disease, 43 with mild cognitive impairment, and 109 people with  
269 idiopathic falls) was similar between the two groups (64 individuals in treadmill training group vs 66 in  
270 treadmill training plus VR group with Parkinson's disease; 20 vs 23 with mild cognitive impairment; and 52 vs  
271 57 with idiopathic falls). The methods of reporting falls used by the participants were similar between groups  
272 ( $p=0.822$ ; data not shown), as was compliance with the interventions ( $p=0.350$ ); of 18 sessions, the mean  
273 number of completed sessions was 16.62 (SD 1.78) in the treadmill training plus VR group and 16.82 (1.81) in  
274 the treadmill training group. Overall, the falls incident rate before the intervention was 11.34 falls (95% CI  
275 9.63–13.34) per 6 months.

276

277 Before training, incident rates were similar ( $p=0.29$ ) between the training groups (table 2). After training, the  
278 incident rate for all participants was 7.10 falls (95% CI 5.51–9.14) per 6 months, which was a significant  
279 reduction compared with before training ( $p<0.0001$ ). In the treadmill training plus VR group, the post-training  
280 incident rate was 6.00 falls (95% CI 4.36–8.25) per 6 months ( $p<0.001$  compared with the 6 months before  
281 training). In the treadmill training group, the incident rate decreased to 8.27 falls (95% CI 5.55–12.31) per 6  
282 months, but this reduction was not significant ( $p=0.49$  compared with the 6 months before training). Similarly,  
283 the incident rate was lower after training in the treadmill training plus VR group than in to the treadmill  
284 training alone group (IRR 0.58, 95% CI 0.36–0.96;  $p=0.033$ ; figure 3 and table 2), showing a significant  
285 advantage for treadmill training plus VR compared with treadmill training. Adjustment for MMSE scores did not  
286 affect the incident rate ratio (data not shown).

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

291 Immediately after training, gait speed under usual and obstacle negotiation walking conditions improved (both  
292  $p<0.0001$ ) in both training groups. Gait variability during obstacle negotiation was significantly lower (ie,  
293 better) in the treadmill training plus VR group than in the treadmill training group. Obstacle clearance was  
294 greater after training in the treadmill training plus VR group than in the treadmill training group. Cognitive  
295 function outcomes improved similarly in both training groups. Scores on the SPPB also improved in both  
296 groups, however, significantly larger gains for the gait and balance components were achieved in the treadmill  
297 training plus VR group than in the treadmill training group. Conversely, self-reported daily life activity did not  
298 change after training in either arm ( $p=0.128$  in treadmill training group;  $p=0.211$  in treadmill training plus VR  
299 group).

300 Several measures were better in the treadmill training plus VR group than in the treadmill training group, even  
301 at the 6 month follow-up. These outcomes included endurance, obstacle clearance, mobility (ie, SPPB scores),  
302 and quality of life (table 3). Training effects at the end of training and the end of follow-up were generally  
303 larger in the treadmill training plus VR group among the patients with Parkinson's disease and the participants  
304 with idiopathic falls (effect sizes  $r=0.08$ – $0.99$ ); in the subgroup with mild cognitive impairment, the differences  
305 between treadmill training plus VR and treadmill training alone were less consistent, possibly because of the  
306 sample size (appendix). Variability in the Parkinson's disease group might be related to the differences in  
307 phenotype or disease manifestation within each of the groups.

308 28 adverse events were reported overall, with 24 occurring in participants who completed a minimum of three  
309 training sessions and were thus included in the analysis: all adverse events led to discontinuation. Of the 28  
310 adverse events, there were five serious adverse events, which consisted of one death from natural causes  
311 (treadmill training group), one stroke (treadmill training plus VR group), one head injury resulting from a car



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

320 In prespecified exploratory analyses, we examined the falls incident rate after training in the three participant  
321 subgroups. Among the participants with Parkinson's disease, the incident rate was lower in the treadmill  
322 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  
323 persisted after adjusting for disease severity (0.47, 0.25–0.89;  $p=0.021$ ). Conversely, incident rate after training  
324 did not differ significantly between groups among the people with idiopathic falls ( $p=0.10$ ) or the participants  
325 with mild cognitive impairment ( $p=0.99$ ). The lack of effect among the people with idiopathic falls might be  
326 related to an imbalance in pretraining values (appendix).

327 We conducted a prespecified secondary analysis of falls status (ie, whether a participant had  $\geq 2$  falls in a given  
328 time period). Before training, all participants could be classed as having had multiple falls, as per the inclusion  
329 criterion of at least two falls in the 6 months before the study. After training, 171 (61%) of 282 participants  
330 reported no falls or only one fall and were therefore no longer classed as having multiple falls (table 2). This  
331 change in falls status occurred in all three subgroups and in both training groups (all  $p<0.0001$ ). The greatest  
332 change in falls status was in subgroups of participants with mild cognitive impairment and the people with  
333 idiopathic falls; only 34 (22%) of these 152 participants (12 [28%] of 43 participants with mild cognitive  
334 impairment and 22 [20%] of 109 participants with idiopathic falls) had multiple falls during the 6 months after  
335 the intervention. Among the 130 participants with Parkinson's disease, 77 (59%) were defined as having had  
336 multiple falls after training, a significantly smaller proportion than before training ( $p<0.0001$ ).

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

341

## 342 Discussion

343 To our knowledge, this study is the first to investigate the effects of an intensive treadmill-based intervention  
344 with and without a VR component on fall rates in an older adult population with a high risk of falls. Both  
345 treadmill training interventions significantly improved markers of fall risk and fall rates were lowered for both  
346 interventions compared with values from before training, emphasizing the therapeutic value of the active  
347 control intervention (ie, treadmill training alone). Nonetheless, comparisons within the training groups showed  
348 that the reduction in fall rates was only significant in the treadmill training plus VR group and not in the  
349 treadmill training group. Consistent with this finding, a direct comparison of the two training groups showed  
350 that the treadmill training plus VR intervention had a significant, positive effect on the incident rate of falls, the  
351 primary outcome, and fall risk (gait variability during obstacle negotiation and obstacle clearance), improving  
352 both to a larger degree than that seen in those who trained on the treadmill without the virtual reality  
353 component. In the treadmill training plus VR arm, the fall incident rate decreased from 11.92 falls per 6 months  
354 before training to 6.00 falls per 6 months after training, showing the ability of this multimodal approach to  
355 substantially reduce the number of falls in this high-risk population.

356 Many older adults are deconditioned, so it is not surprising that the intensive treadmill training was associated  
357 with improved outcomes in our high-risk participants, possibly by facilitating more effective motor control. This  
358 finding concurs with results from metaanalyses on the effect of exercise on fall risk in older adults and patients

359 with Parkinson's disease.<sup>28,33</sup> Nonetheless, the rate of falls after training was 42% lower in the treadmill training  
360 plus VR arm than in the active control group of treadmill training alone. The added value of the VR component  
361 might be explained by the nature of the training. The motor-cognitive intervention provided by the VR  
362 implicitly trained obstacle negotiation strategies in a complex, enriched environment that requires focused  
363 attention and planning.<sup>11</sup> Executive function and attention have important roles in the regulation of gait,  
364 especially in complex situations such as obstacle negotiation.<sup>34,35</sup> Although the cognitive outcome measures  
365 were not sensitive enough to detect differences between training groups, everyday activities such as obstacle  
366 avoidance, which do require cognitive function, improved to a larger extent with the treadmill training plus VR  
367 intervention than they did with treadmill training alone. Training in the VR environment might have enhanced  
368 performance during attention demanding and challenging situations, thereby contributing to real-world fall  
369 avoidance during the 6 month follow-up period.

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

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

397 Our results suggest that treadmill training plus VR training has an advantage over treadmill training alone,  
398 especially in people with Parkinson's disease. For this subgroup, training with virtual reality reduced the risk of  
399 falls by nearly 60% (IRR 0.45) more than in the treadmill training intervention. This is noteworthy given the high  
400 fall rates in patients with this neurodegenerative disease.<sup>2</sup> It is possible that people with Parkinson's disease  
401 benefited most because their baseline rate of falls was highest. Another explanation could be that falls  
402 improved particularly in this subgroup because the pathophysiology of falls in Parkinson's disease usually  
403 involves the interplay between motor and cognitive deficits; both domains were clearly affected among the  
404 participants with Parkinson's disease in this study, and both domains were improved by the treadmill training  
405 plus VR training. By contrast, both training interventions reduced fall risk and improved falls status in the older  
406 adults and individuals with mild cognitive impairment subgroups. Possibly, the underlying cause of falls in these  
407 subgroups more heavily involved motor components and hence both treatment approaches were effective.

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

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

454

455 **Contributors**

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

461 **Declaration of interests**

462 All authors report receiving support from the European Commission for the conduct of this study. LR also  
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476 data and vouch for the fidelity of the trial to the protocol.

477

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580

581 **AUTHORS CONTRIBUTIONS**

582 AM, LR, MOR, BRB, EP, LA, GA, AN, and JMH participated in the conception, study design and obtaining funding  
583 (FP7 EC consortium). IM, SDD, LA, FN, KD and EB contributed to data collection, data processing, interpretation  
584 of results, and drafting the manuscript. AM and JMH contributed to the data analysis. AM, LR, MOR, BRB, EP,  
585 LA, GA, AN, NG and JMH contributed to the interpretation of the results, drafting of the manuscript, and made  
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587

588 **DECLARATION OF INTERESTS**

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

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601 **RESEARCH IN CONTEXT**

602 **Evidence before this study**

603 We searched PubMed and the Cochrane Database for relevant articles published from Jan 1, 1980, to Dec 31,  
604 2015. We used the keywords falls, prevention training, aging, older adults, and Parkinson's disease. The search  
605 resulted in the identification of several reviews and meta-analyses. Many intervention programs based on  
606 reported multiple risk factors have been proposed and evaluated. However, despite the extensive knowledge  
607 on fall risk obtained in recent years, there is no consensus as to the most efficacious or optimal treatment  
608 approach. To date, the impact on fall risk from common treatment approaches tends to be small and the  
609 reported changes are largely focused on motor aspects with limited long-term retention. Furthermore, most  
610 trials compared a fall prevention intervention with no intervention or an intervention not expected to reduce  
611 falls, stressing the need for studies with an active control comparison. A paucity of studies targeting  
612 participants with cognitive deficits was also noted. In addition, recent work on the role of the central nervous  
613 system in mobility calls for multi-modal interventions that target multiple pathways simultaneously, using an  
614 adaptive and individually tailored treatment in an enjoyable and challenging environment to increase  
615 adherence and maintenance. The present study addresses these gaps in previous fall risk interventions.

616 **Added value of this study**

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

627 **Implications of all available evidence**

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

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<b>Table 1: Subject characteristics*</b>			
	<b>TT (n=136)</b>	<b>TT+VR (n=146)</b>	<b>P-value</b>
<b>Age [yrs]</b>	73.3±6.4 73.0 (61.0 - 89.0)	74.2±6.9 74.0 (60.0 - 89.0)	0.244
<b>Gender [M / F]</b>	84 / 52 61.8% / 38.2%	98 / 48 67.1% / 32.8%	0.625
<b>Education [yrs]</b>	12.9±3.9 13.0 (3.0 - 30.0)	13.1±4.00 13.0 (5.0 - 22.0)	0.671
<b>Fall history [number of falls in 6 months prior to the intervention]</b>	10.7±35.6 2.5 (2.0 - 260.0)	11.9±39.5 3.0 (2.0 - 300.0)	0.786
<b>Mini Mental State Examination [max 30]</b>	28.2±1.7 28.5 (24.0 - 30.0)	27.8±1.8 26 (22.0 - 30.0)	0.092
<b>Number of Prescription Medications</b>	6.1±3.5 6 (1-19)	6.3±3.9 5 (1- 20)	0.703
<b>Gait speed during 2 Minute Walk test [m/sec]</b>	1.02±0.27 1.04 (0.21- 1.70)	1.02±0.28 1.04 (0.21- 1.70)	0.662

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\*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 <sup>time</sup>	1.06 <sup>time</sup>	-0.012 (-0.045, 0.022)			
		6M follow-up	1.05 <sup>time</sup>	1.05 <sup>time</sup>	-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 <sup>time</sup>	-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 <sup>time</sup>	1.02 <sup>time</sup>	0.014 (-0.019, 0.048)			
		6M follow-up	0.98 <sup>time</sup>	0.98 <sup>time</sup>	0.022 (-0.014, 0.046)			
	Gait speed variability obstacle negotiation (%)	Pre-training	16.62	16.78	0.156 (-1.149, 1.461)	<b>0.018</b>	<0.001	0.020 <sup>3</sup>
		Post-training	15.97 <sup>time</sup>	13.92 <sup>time; arm</sup>	-2.044 (-3.363, -0.725)			
		6M follow-up	14.84	13.90 <sup>time</sup>	-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)	<b>0.002</b>	0.040	0.844 <sup>3</sup>
		Post-training	32.03	33.74 <sup>time</sup>	1.244 (-0.055, 2.544)			
		6M follow-up	30.56 <sup>time</sup>	33.06 <sup>arm</sup>	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 <sup>2,3</sup>	
	Post-training	128.48 <sup>time</sup>	132.49 <sup>time; arm</sup>	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 <sup>time</sup>	94.07 <sup>time</sup>	-0.722 (-2.277, 0.831)			
		6M follow-up	96.05 <sup>time</sup>	95.36 <sup>time</sup>	-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 <sup>time</sup>	93.26	-0.365 (-2.482, 1.752)			
		6M follow-up	94.86 <sup>time</sup>	95.12 <sup>time</sup>	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 <sup>time</sup>	9.61 <sup>time</sup>	0.151 (-0.186, 0.488)			
		6M follow-up	8.79	9.17 <sup>arm</sup>	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 <sup>time</sup>	2.37 <sup>time</sup>	-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)	<b>0·030</b>	<0·001	0·032 <sup>3</sup>
		Post-training	3·33 <sup>time</sup>	3·41 <sup>time</sup>	0·078 (-0·101, 0·258)			
		6M follow-up	3·09	3·39 <sup>time; arm</sup>	0·294 (0·106, 0·483)			
	SPPB gait	Pre-training	3·52	3·55	0·037 (-0·089, 0·164)	<b>0·032</b>	<0·001	0·238 <sup>3</sup>
		Post-training	3·68 <sup>time</sup>	3·80 <sup>time; arm</sup>	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)	<b>0·033</b>	<0·001	0·008 <sup>1</sup>
		Post-training	57·73	60·56 <sup>time</sup>	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)	<b>0·041</b>	0·072	0·494 <sup>1</sup>
		Post-training	70·43	72·35 <sup>time</sup>	1·924 (-1·037, 4·886)			
		6M follow-up	69·94	72·41 <sup>time</sup>	2·468 (-0·629, 5·567)			

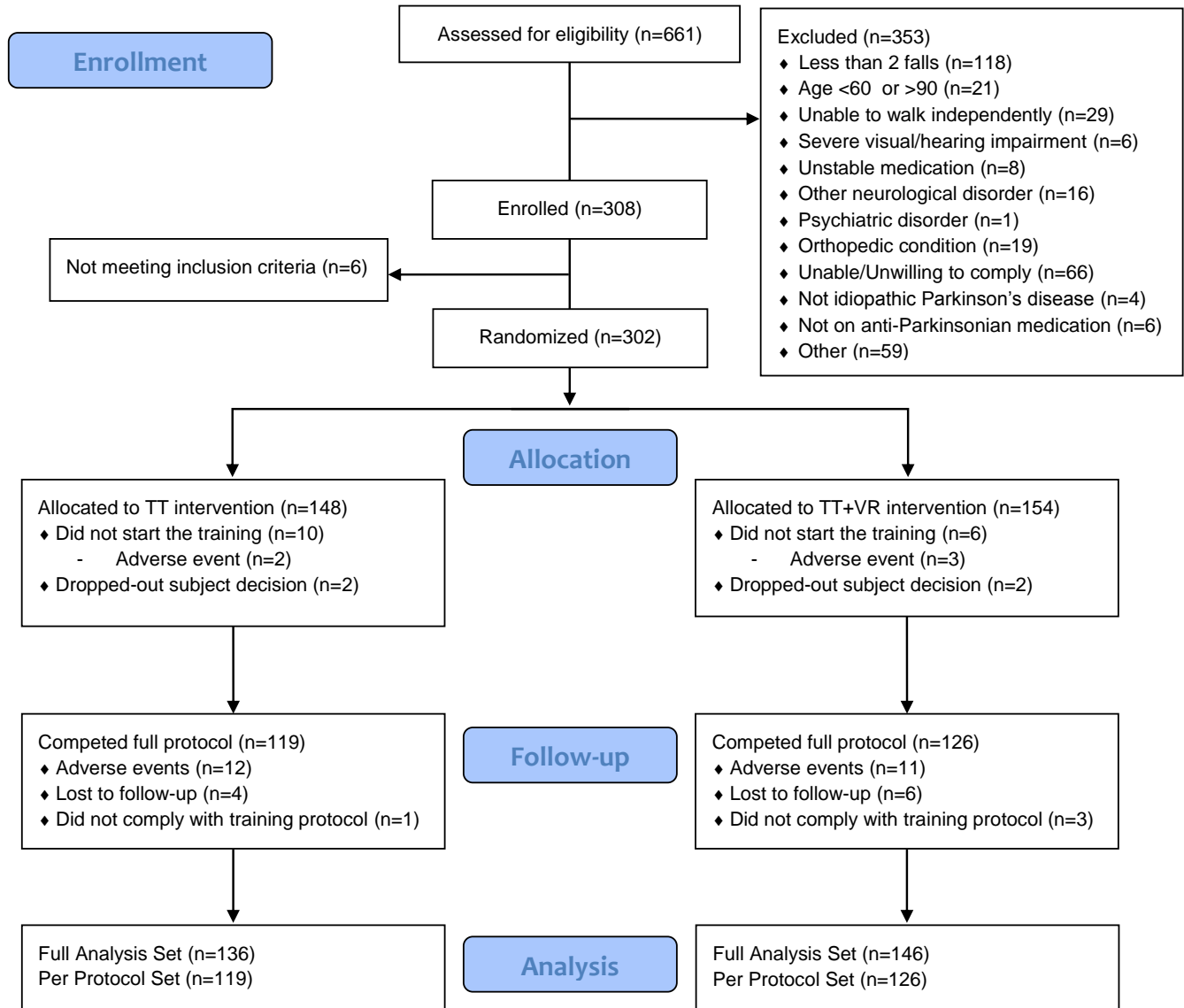
For the sake of brevity, results at the 1 month time point are not shown. In general, values at this time point were in between those measured at the post and 6 month testing assessments. Pre-training, these secondary outcome measures were similar in the TT+VR and TT arms ( $p > 0.12$ ). The three p-values 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. <sup>time</sup> indicates a significant within training arm effects of time, compared to pre-training values. <sup>arm</sup> 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.

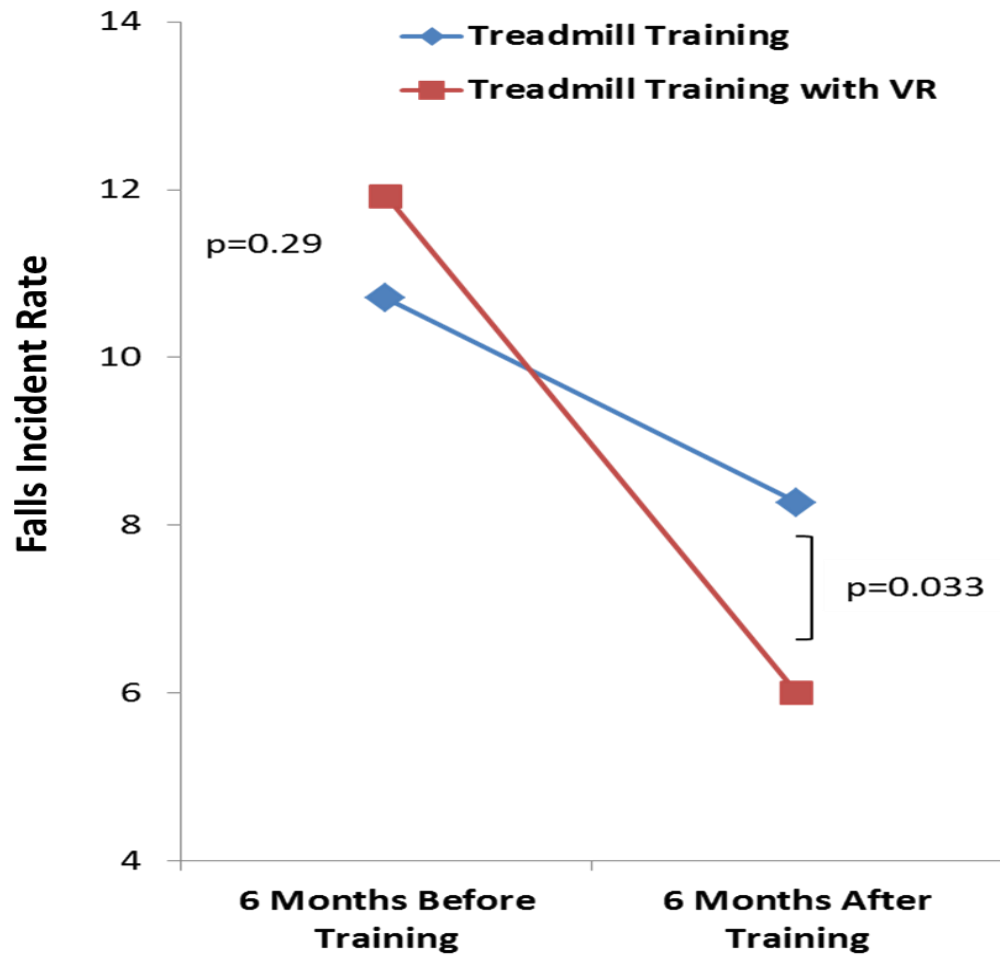
		Pre-training				Post-training			
		All subjects	Elderly	MCI	PD	All subjects	Elderly	MCI	PD
Total # of falls	TT	1456	168	57	1231	1083	45	25	1013
	TT+VR	1741	460	76	1205	817	276	52	489
# and % of recurrent fallers (≥ 2)	TT	136 (100%)	52 (100%)	20 (100%)	64 (100%)	49 (36.0%)	8 (15.4%)	6 (30.0%)	35 (54.7%)
	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"<sup>11</sup>.



**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.